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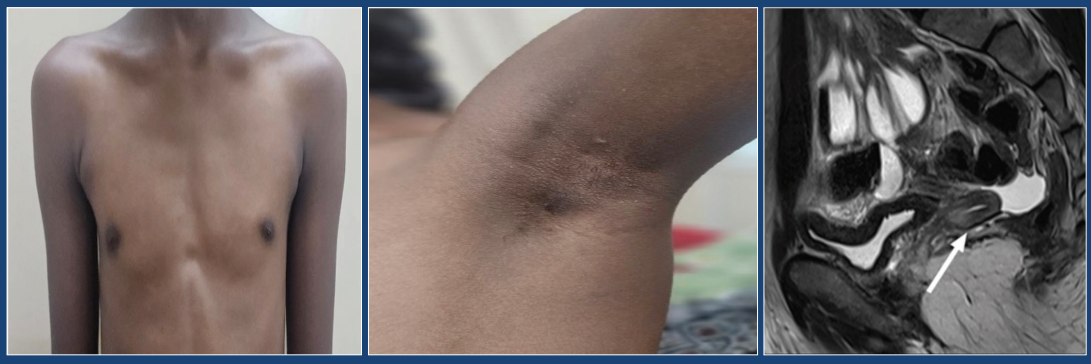

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Cover Picture: Aparna Setty et al. Ovotesticular disorder with gonadal dysgenesis

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Aims and Scope

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The ''Journal of the Turkish-German Gynecological Association'' (E-ISSN 1309-0380; Abbreviated as "J Turk Ger Gynecol Assoc") is the official, open access publication of the Turkish-German Gynecological Education and Research Foundation and the Turkish-German Gynecological Association. Formerly named "ARTEMIS", the journal is published quarterly (March, June, September, December) in English and publishes original peer-reviewed articles, reviews, and commentaries in the fields of Gynecology, Gynecologic Oncology, Endocrinology & Reproductive Medicine and Obstetrics. Case reports are not accepted for publication. Reviews will be considered for publication only if they are prepared by authors who have at least three published manuscripts in international peer reviewed journals and these studies should be cited in the review. Otherwise only invited reviews will be considered for peer review from qualified experts in the area.

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degree(s) of the author(s) and source(s) of the work or study, a short title (running head) of no more than 50 characters. The name, address, telephone (including the mobile phone number) and fax numbers and e-mail address of the corresponding author should be listed on the title page.

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State concisely the purpose and rationale for the study and cite only the most pertinent references as background.

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Present the detailed findings supported with statistical methods. Figures and tables should supplement, not duplicate the text; presentation of data in either one or the other will suffice. Emphasize only your important observations; do not compare your observations with those of others. Such comparisons and comments are reserved for the discussion section.

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Contents

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Editorial

Dear Colleagues,

It is my great pleasure to introduce the third issue of the "Journal of the Turkish-German Gynecological Association (J Turk Ger Gynecol Assoc)" in the publishing year of 2026. This issue is consisted of six articles that we hope you will read with interest. Also you may have the oppurtunity to read two quizzes. Here we share some of our favorite articles that were published in this issue of the journal.

One of the most commonly performed surgical procedures involving the female reproductive system in gynecologic practice is the hysterectomy. Both patients and surgeons can benefit from robotic-assisted hysterectomy in a number of ways. Improved ergonomics, tremor filtration, increased instrument articulation, and improved three-dimensional imaging enable precision surgical procedures with less tissue damage. A study comparing the safety and efficacy of unidirectional barbed (V-Loc) sutures versus conventional polyglactin 910 (Vicryl) sutures for robotic vaginal vault closure, will be available for you to read.

Adolescents with mental disorders (MD) virtually always become pregnant inadvertently. This risk is increased by impulsivity, a lack of planning and behavioral control, and the challenge of consistently utilizing contraceptives. The quarterly injectable depot medroxy-progesterone acetate (DMPA) and long-acting reversible contraceptives, which include hormonal and non-hormonal intrauterine devices (IUD) and subcutaneous implants, are among the most popular methods of birth control among teenagers with MD. You will also have the opportunity to read a study evaluating the continuity and satisfaction rate with the use of hormonal IUD and quarterly DMPA for 12 months in adolescents with MD.

Dear Participants,

I would also like to invite you to join us for our prestigious 16th Turkish-German Gynecology Congress which will be held in Antalya between 28 April-2 May 2027. As of before, our congress will be held to the highest scientific standards with a rich scientific program and pre-congress courses.

The XVI. Turkish German Gynecology Congress will reward the best 3 abstracts. The purpose of this reward is to show our colleagues our appreciation for their productivity and also motivate our young colleagues for the forthcoming years. Also the best presentation which will be elected by the Scientific Committee will receive "Dr. Aysun - Cihat Ünlü Special Reward" of 50000 TL.

Dear Esteemed Readers, Authors and Reviewers,

The Scopus CiteScore of the J Turk Ger Gynecol Assoc was announced as 2.4 in 2024 and 2.5 in 2025. The 2024 CiteScore was calculated based on 340 citations received by 143 documents published between 2021 and 2024, while the 2025 CiteScore was calculated based on 316 citations received by 124 documents published between 2022 and 2025. Based on these data, the journal's CiteScore increased slightly but positively from 2.4 to 2.5. This increase indicates that, despite the decrease in the number of documents within the evaluation period, the journal maintained its citation performance and sustained its visibility within Scopus. In terms of category performance, the journal ranked #113 out of 210 journals and was placed in the 46th percentile in the Obstetrics and Gynecology category in 2024. In 2025, it ranked #116 out of 218 journals and was placed in the 47th percentile. This result shows that the journal largely maintained its visibility within the category and achieved a slight improvement in percentile ranking. The 2026 CiteScoreTracker is currently 1.9. This is an interim indicator calculated based on 180 citations and 97 documents recorded to date. Since the Tracker value is updated monthly throughout the year, it should not be considered the final CiteScore result; it may change as new citations are received during the year.

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Sincerely,

Prof. Cihat Ünlü, M.D.
Editor in Chief of J Turk Ger Gynecol Assoc
President of TGGF

Unidirectional barbed versus single layer conventional suture for vaginal cuff closure in robotic hysterectomy: retrospective single-center study

Anupama Bahadur, Megha Ajmani, Rajlaxmi Mundhra, Lakhwinder Singh, Latika Chawla, Ayush Heda

Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, Rishikesh, India

Abstract

Objective: Successful vaginal cuff suturing remains a major challenge in robotic hysterectomy. This study compared the vault closure time by using Vicryl (polyglactin 910) and barbed (V-Loc) sutures.

Material and Methods: This retrospective study included patients undergoing robotic hysterectomy for benign disease over three years. Patients were grouped according to the suture used for vaginal vault closure. Surgical videos and hospital records were reviewed to obtain operative details, perioperative outcomes, and postoperative complications.

Results: A total of 297 patients were included in final analysis with 106 (35.7%) patients in the Vicryl group and 191 (64.3%) patients in the barbed suture group. In the barbed compared to Vicryl group, the robotic vault closure time (6.84±1.42 vs. 9.93±2.77 minutes), average number of stitches used for vault closure (5.02±0.57 vs. 5.61±0.75), and time taken per stitch (1.36±0.3 vs. 1.75±0.43 minutes) were significantly lower. Operative time, anesthesia duration, and hospital stay were also significantly lower in the barbed group. On multivariable linear regression analysis, barbed suture use remained independently associated with shorter vault closure time (β =8.47 minutes, 95% confidence interval 5.46-11.48; p<0.001), while age, body weight, body mass index, parity, and preoperative anemia were not independently associated with vault closure time. On sexual function assessment, the overall score of female sexual function index in barbed (29.02±4.85) was significantly higher than the Vicryl (27.39±7.35) suture group (p=0.049).

Conclusion: Barbed sutures may represent a feasible and time-efficient option for robotic vaginal vault closure; however, prospective randomized studies with longer follow-up are required to confirm their safety, and impact on functional outcomes. [J Turk Ger Gynecol Assoc. 2026; 27(3): 157-64]

Keywords: Minimally invasive, robotic surgery, hysterectomy, vault closure time

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Introduction

Hysterectomy represents one of the most commonly performed operative procedures involving the female reproductive tract in gynecologic practice. Data from the World Health Organization indicate that approximately 1.54 million hysterectomies were performed worldwide in 2016. In India, the prevalence of hysterectomy is estimated to be around 11.35%, with abnormal uterine bleeding (AUB) and uterine fibroids being the predominant indications (1). The procedure is most frequently undertaken for excessive menstrual bleeding (28.94%), fibroid uterus (24.29%), uterine prolapse (15.99%), uterine disorders

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(8.30%), postpartum hemorrhage (4.59%), malignancy (2.15%), and other causes (9.02%).

A major advance in gynecologic surgery over recent decades has been the shift from open surgery to minimally invasive techniques. The introduction of the da Vinci Surgical System and its approval by the US Food and Drug Administration (FDA) in 2005 marked a significant milestone in this evolution (2,3). Initially adopted in specialties such as urology and cardiac surgery, robotic-assisted techniques have gained widespread acceptance in gynecology. Despite ongoing concerns regarding cost and healthcare resource utilization, robotic surgery has seen rapid expansion due to its technical advantages and favorable patient outcomes (4,5).

Robotic-assisted hysterectomy offers several benefits for both surgeons and patients. Enhanced three-dimensional visualization, tremor filtration, improved ergonomics, and greater instrument articulation allow for precise surgical maneuvers with reduced tissue trauma. These features contribute to decreased intraoperative blood loss, lower postoperative pain, faster recovery, shorter hospitalization, and improved quality of life. Consequently, robotic platforms have been approved and widely utilized for a variety of gynecologic procedures, including hysterectomy, myomectomy, radical hysterectomy, prolapse repair, tubal anastomosis, and surgery for endometriosis (5-7).

Despite these advantages, closure of the vaginal cuff remains one of the technically demanding steps in robotic hysterectomy. Minimally invasive approaches are associated with a higher incidence of vaginal cuff-related complications, particularly vaginal cuff dehiscence, compared with abdominal or vaginal routes (8). Vaginal cuff dehiscence is defined as a full-thickness separation of the vaginal cuff and has been reported in 1.0-4.1% of minimally invasive hysterectomies performed using conventional suturing techniques (9,10). Several patient-related factors, including smoking, diabetes mellitus, advanced age, immunosuppression, and gynecologic malignancy, have been implicated in increasing this risk (10). In addition, the use of thermal energy during colpotomy may result in tissue necrosis, delayed healing, cuff cellulitis, and subsequent dehiscence (11-13).

Barbed sutures, characterized by unidirectional barbs along the suture line, maintain tissue approximation without the need for knot tying. Emerging evidence suggests that barbed sutures are comparable to conventional sutures in terms of safety and tolerability, while potentially reducing operative time during minimally invasive vaginal cuff closure (14). The present study aimed to compare the safety and efficacy of unidirectional barbed (V-Loc) sutures versus conventional polyglactin 910 (Vicryl) sutures for robotic vaginal vault closure, using a single-layer continuous suturing technique performed by the same surgeon.

Material and Methods

Study design

This was a retrospective study done in patients who underwent robotic hysterectomy for benign disease at our institution over three years from March 2018 to July 2021. This retrospective study was conducted after approval from the Institutional Ethics Committee of All India Institute of Medical Sciences, Rishikesh (approval no.: AIIMS/IEC/19/1165; date: November 29, 2019). As all data were collected from existing records, the requirement for individual informed consent was waived by the committee, and all patient information was anonymized to ensure confidentiality. Records were obtained from the surgical videos (for various surgical timings) and hospital database, comparing unidirectional barbed suture (V-Loc) and polyglactin 910 (Vicryl) suture for the closure of the vaginal vault in patients with total robotic hysterectomy for benign pathologies (Figure 1).

As per the standard closure technique using two different materials, patients were segregated and divided into two groups, a barbed group and a Vicryl group, depending on type

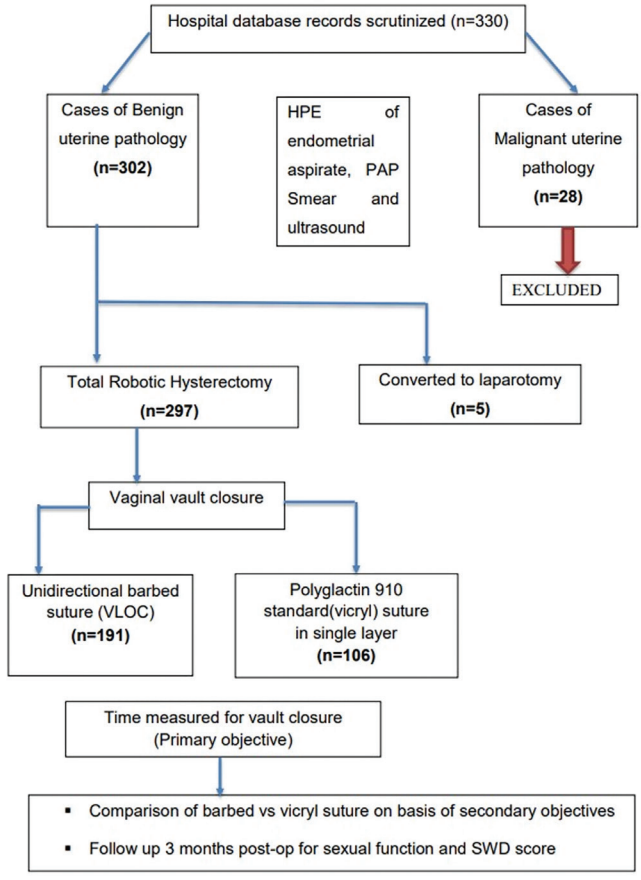

Figure 1. Flowchart of the study population
HPE: Histopathological examination, PAP: Papanicolaou smear/test, SWD: Satisfaction with decision

of suture used for vault closure after robotic hysterectomy. Technique and material by necessity were not blinded to the surgeon. Any record lacking vital information was excluded. Through the hospital database records, operative notes, discharge summaries, the entire details of intraoperative and postoperative complications were obtained. All data and records generated during this study were anonymized and kept confidential as per Institutional policies on subject privacy and data and records would not be used for any purpose other than conducting the study. Every record was reviewed to ascertain whether the subject was eligible for the study, "enrolled" and met the enrolment criteria and had the necessary data to be included in the analysis was "evaluable."

Outcome measures

The primary objective analysed was the measurement of cuff closure time by use of unidirectional barbed (V-Loc) suture vs polyglactin 910 (Vicryl) sutures for vaginal vault closure. Various secondary objective measures analysed included intraoperative measures such as average blood loss, operative time, number of stitches, and hospital stay, and postoperative measures like vaginal vault dehiscence, vault hematoma, and also sexual function assessment at three months postoperatively, using the female sexual function index (FSFI) tool.

Duration of anesthesia was defined as the duration from induction of anesthesia until reversal from anesthesia and it included docking time, console time, vault closure time, and time required for specimen extraction and skin suturing and reversal from anesthesia. Operative time was the duration from incision time until port closure time and was the time taken for the hysterectomy procedure. Vaginal spotting was defined as bloody vaginal discharge that resolves spontaneously without requiring special interventions. In contrast, vaginal bleeding was defined as postoperative bleeding from the vaginal stump necessitating extra outpatient visits, transfusions, or additional sutures. Vaginal cuff dehiscence as a visually confirmed opening of the vaginal stump, potentially with or without herniation of visceral organs. The 3-month post-operative sexual function assessment was elicited. The satisfaction with the decision was assessed using the satisfaction with decision (SWD) score.

Statistical analysis

Data were entered into Microsoft Excel, and statistical analysis was performed using the Statistical Package for Social Sciences (SPSS), version 21.0 (IBM Inc., Armonk, NY, USA). Categorical variables are summarized as frequencies and percentages. Continuous variables are expressed as mean ± standard deviation (SD) or as median with interquartile range, as appropriate. Comparisons of continuous variables were carried out using the independent t-test, while categorical variables were analyzed using the chi-square test or Fisher's exact test. To account for baseline differences and potential confounding due to the retrospective and non-randomized design, a multivariable linear regression analysis was performed. Adjusted beta coefficients with 95% confidence intervals (CIs) were calculated. A p-value <0.05 was considered statistically significant.

Results

Baseline characteristics

The present study was conducted at a tertiary care centre and 302 patients who had undergone robotic total hysterectomy without any other simultaneous procedure for a benign cause with uterine size <12 weeks meeting inclusion criteria were retrospectively analysed. Five cases were excluded as they were converted to laparotomy. Thus 297 cases were included in the final analysis (Figure 1). Surgical details regarding the type of suture and time required for surgery were obtained by the video database. Various demographic details of the study population are presented in Table 1.

In the majority [191 (63.25%)] of patients, the type of suture used was barbed, with 106 (35.10%) patients in the Vicryl group, and for five patients' surgery was converted to laparotomy. A significant difference was seen in weight (kg) between the barbed group and the Vicryl group [64.33±8.66 and 61.87±9.1 ($p=0.017$)]. No significant difference was seen in the mean age, height, body mass index (BMI), menopausal status, parity, and previous history of cesarean deliveries between the two groups. The proportion of patients with anemia was significantly higher in the barbed group compared to the Vicryl group [15.71% vs. 6.60% respectively ($p=0.023$)]. The distribution of other significant co-morbidities was comparable between the two groups. Moreover, the distribution of indication for hysterectomy and final histopathology were comparable between barbed group and Vicryl groups. The most common indication for hysterectomy in our study was AUB due to fibroid uterus (n=145) followed by adenomyosis (n=66) and adnexal masses (n=28) (Table 2).

Outcome measures

The mean ± SD of vault closure time (minutes) in the Vicryl group was 9.93±2.77 which was significantly higher when compared to the barbed group (6.84±1.42) ($p<0.001$). The mean ± SD of the number of stitches taken for vault closure in the Vicryl group was 5.61±0.75 and was also significantly greater compared to the barbed group (5.02±0.57) ($p<0.001$). Mean ± SD of time taken per stitch (minutes) in Vicryl group was 1.75±0.43 and significantly longer compared to barbed group (1.36±0.3) ($p<0.001$). Mean operative time, duration of

anesthesia, and length of hospital stay were also significantly longer in Vicryl group compared to the barbed group, whereas mean blood loss and blood transfusion rates were not different between two groups (Table 3).

On multivariable linear regression analysis, barbed suture use was independently associated with vault closure time (β =8.47 minutes, 95% CI 5.46-11.48; p<0.001). Age, body weight, BMI, parity, and preoperative anemia status were not independently associated with vault closure time.

Various perioperative (intraoperative and postoperative) complications in both the groups are given in Table 4. There was no significant difference in perioperative complications between the two groups.

On sexual function assessment using the FSFI at three months postoperatively, a significant difference was seen in the lubrication score, pain score, and total score in favor of barbed sutures between the barbed group and Vicryl group (p<0.05) (Table 5). Mean ± SD of SWD scale at post-operative three months in the barbed group was 27.58±4.46 and Vicryl group was 26.9±3.21 with no significant difference between them (p=0.165). However, preoperative baseline sexual function data were not available for comparison.

Table 1. Demographic characteristics of the study population

Demographic characteristic	Barbed n=191 n (%)	Vicryl n=106 n (%)	Total n=297 n (%)	p-value
Age (years)*	45.14±6.15	45.16±6.5	45.15±6.27	0.98
Weight (kg)*	64.33±8.66	61.87±9.1	63.45±8.88	0.017
Height (cm)*	156.06±6.02	155.75±4.72	155.95±5.58	0.58
Body mass index (kg/m²)*	26.5±3.85	25.58±4.15	26.17±3.98	0.055
Menopausal status				0.329
Premenopausal	172 (90.05)	99 (93.40)	271 (91.25)	
Postmenopausal	19 (9.95)	7 (6.60)	26 (8.75)	
Parity*	2.93±1.39	3±1.25	2.95±1.34	0.652
Previous cesarean section				0.488#
None	180 (94.24)	102 (96.23)	282 (94.95)	
One	7 (3.66)	4 (3.77)	11 (3.70)	
Two	4 (2.09)	0 (0)	4 (1.35)	
Co-morbidities				
Anemia	30 (15.71)	7 (6.60)	37 (12.46)	0.023
Diabetes mellitus	8 (4.19)	6 (5.66)	14 (4.71)	0.566
Hypertension	17 (8.90)	8 (7.55)	25 (8.42)	0.687
Hypothyroidism	13 (6.81)	9 (8.49)	22 (7.41)	0.595
Others	3 (1.52)	6 (5.66)	9 (3.03)	
Indications for hysterectomy				0.177**
Leiomyoma	94 (49.21)	51 (48.11)	145 (48.82)	
Adenomyosis	45 (23.56)	21 (19.81)	66 (22.22)	
Adenomyosis with leiomyoma	1 (0.52)	2 (1.89)	3 (1.01)	
Endometrial polyp	10 (5.24)	6 (5.66)	16 (5.39)	
Postmenopausal bleeding	13 (6.81)	5 (4.63)	18 (6.06)	
AUB (E)	5 (2.62)	8 (7.55)	13 (4.38)	
Adnexal mass	17 (8.90)	11 (10.38)	28 (9.43)	
UV descent	6 (3.14)	2 (1.89)	8 (2.69)	
Procedures performed				<0.001#
TRH	20 (10.47)	21 (19.81)	41 (13.80)	
TRH + bilateral salpingectomy	103 (53.93)	30 (28.30)	133 (44.78)	
TRH + bilateral salpingo-oophorectomy	68 (35.60)	55 (51.89)	123 (41.41)	

*Mean ± SD, **Fisher's exact test, #chi-square test, TRH: Total robotic hysterectomy, SD: Standard deviation, AUB: Abnormal uterine bleeding, UV: Uterovaginal

Discussion

This retrospective analysis evaluated patients who underwent robotic hysterectomy for benign indications at our institution between March 2018 and July 2021. The findings demonstrate that the use of barbed sutures for vaginal vault closure was associated with a significant reduction in vault closure time, overall operative duration, anesthesia time, and length of hospital stay when compared with conventional Vicryl sutures. The association between suture material and vault closure time remained significant after adjustment, suggesting an independent effect. Nonetheless, residual confounding cannot be completely excluded. In addition, postoperative sexual function outcomes appeared more favorable in the barbed suture group, however these findings should be considered exploratory. The higher postoperative FSFI scores observed in the barbed suture group may reflect differences in postoperative recovery or unmeasured baseline factors rather than a direct effect of suture material.

Several published studies have examined vaginal cuff closure following robotic or laparoscopic hysterectomy, primarily focusing on complications, such as vaginal cuff dehiscence (8,10-13). However, literature specifically analyzing the impact of different suture materials on vault closure time and its contribution to total operative duration remains limited. In our study, barbed sutures reduced vaginal vault closure time by approximately 3.09 minutes compared with Vicryl sutures, a finding that aligns with previously published reports.

Table 2. Distribution of final histopathology of the study population

Final histopathology	Barbed n=191 n (%)	Vicryl n=106 n (%)	Total n=297 n (%)	p-value
Leiomyoma	92 (48.17)	43 (40.57)	135 (45.45)	0.087*
Adenomyosis	40 (20.94)	21 (19.81)	61 (20.54)	
Proliferative endometrium	18 (9.42)	10 (9.43)	28 (9.43)	
Endometrial polyp	11 (5.76)	8 (7.55)	19 (6.40)	
Endometriosis	9 (4.71)	7 (6.60)	16 (5.39)	
Leiomyoma + adenomyosis	2 (1.05)	7 (6.60)	9 (3.03)	
Simple endometrial hyperplasia	3 (1.57)	3 (2.83)	6 (2.02)	
Atrophic endometrium	4 (2.09)	1 (0.94)	5 (1.68)	
Hemorrhagic cyst	2 (1.05)	2 (1.89)	4 (1.35)	
Disordered endometrium	0 (0)	3 (2.83)	3 (1.01)	
Cystic teratoma	3 (1.57)	0 (0)	3 (1.01)	
Normal endomyometrium	3 (1.57)	0 (0)	3 (1.01)	
Adenocarcinoma endometrium	2 (1.05)	0 (0)	2 (0.67)	
Cystic glandular hyperplasia	0 (0)	1 (0.94)	1 (0.34)	
Mucinous cystadenoma	1 (0.52)	0 (0)	1 (0.34)	
Benign Brenner tumor	1 (0.52)	0 (0)	1 (0.34)	
*Fisher's exact test				

Table 3. Various intraoperative parameters of two study groups

Perioperative parameters (mean ± SD)	Barbed n=191	Vicryl n=106	Total n=297	p-value
Vault closure time (in minutes)	6.84±1.42	9.93±2.77	7.95±2.49	<0.001
Number of stitches taken for vault closure	5.02±0.57	5.61±0.75	5.23±0.7	<0.001
Time taken per stitch (minutes)	1.36±0.3	1.75±0.43	1.5±0.4	<0.001
Operative time (minutes)	60.81±13.44	66.26±19.28	62.75±15.96	0.011
Duration of anesthesia (minutes)	90.43±13.01	107.98±17.15	96.7±16.85	<0.001
Average blood loss (mL)	65.42±36.8	65.94±24.15	65.61±32.81	0.883
Blood transfusion rate	0.31±0.74	0.17±0.58	0.26±0.69	0.074
Length of hospital stay (days)	3.87±1.34	4.79±1.26	4.2±1.38	<0.001
SD: Standard deviation				

Kim et al. (14) reported significantly shorter cuff closure times using V-Loc sutures compared to Vicryl in laparoscopic hysterectomy patients (8.84±2.18 vs. 11.66±1.74 minutes). Similarly, Ardovino et al. (15) demonstrated a marked reduction in closure time with bidirectional barbed sutures compared to conventional sutures (3.9 vs. 6.2 minutes). In contrast, Einarsson et al. (16) found no statistically significant difference in vaginal cuff closure time between the two suture types in a randomized study. A systematic review by Smith and Caceres (17) reported reductions in both total operative time and vault closure time with barbed sutures, suggesting that time savings may offset their higher cost.

The observed reduction in suturing time with barbed sutures can be attributed to the elimination of knot tying and the absence of a need for constant traction to maintain suture tension. However, proper handling of barbed sutures, including passage of the needle through the terminal loop, requires specific technical proficiency and may involve a learning curve that influences operative efficiency. Given that vaginal cuff closure is a critical step in robotic hysterectomy, multiple techniques and materials have been explored to optimize outcomes and minimize complications. Unlike conventional sutures, barbed sutures do not require an assistant to maintain tension and allow uniform tissue approximation without knots.

In the present study, patients in the Vicryl group experienced a significantly longer hospital stay compared with those in the barbed suture group. Similar reductions in length of hospital stay with barbed sutures have been reported by Kim et al. (14) and Nawfal et al. (18). Although the median difference between groups was approximately one day, hospital stay is influenced by multiple factors, including baseline comorbidities, operative duration, and postoperative recovery.

Due to the retrospective design of this study, preoperative sexual function could not be assessed. Nevertheless, postoperative

Table 4. Various perioperative complications of the study groups

Complications	Barbed n=191 n (%)	Vicryl n=106 n (%)	Total n=297 n (%)	p-value
Intra-operative complications				
Bladder injury	2 (1.05)	1 (0.94)	3 (1.01)	1.000
Uterine perforation	2 (1.05)	0 (0)	2 (0.67)	0.539
Rectosigmoid injury	1 (0.52)	0 (0)	1 (0.34)	1.000
Post-operative complications				
Fever	5 (2.62)	7 (6.60)	12 (4.04)	0.095
Urinary tract infections	2 (1.05)	4 (3.77)	6 (2.02)	0.191
Vaginal spotting/discharge	3 (1.57)	5 (4.72)	8 (2.69)	0.139
Vaginal bleeding	0 (0)	0 (0)	0 (0)	-
Vaginal dehiscence	0 (0)	1 (0.94)	1 (0.34)	0.357
Post-op ureterovaginal fistula	0 (0)	1 (0.94)	1 (0.34)	0.357
Subcutaneous emphysema	1 (0.52)	0 (0)	1 (0.34)	1.000
Readmission rate	2 (1.05)	4 (3.77)	6 (2.02)	0.191

Table 5. Comparison of female sexual fertility index (after three months postoperatively) between the two groups

Female sexual fertility index (mean ± SD)	Barbed n=191	Vicryl n=106	Total n=297	p-value
Desire score	4.7±1.03	4.42±1.33	4.59±1.16	0.072
Arousal score	4.45±0.96	4.45±1.15	4.45±1.03	0.996
Lubrication score	4.61±0.8	4.22±1.28	4.47±1.02	0.007
Orgasm score	4.78±1.06	4.59±1.4	4.71±1.2	0.203
Satisfaction score	5±0.73	4.9±1.22	4.97±0.94	0.46
Pain score	5.48±0.71	4.81±1.47	5.23±1.1	<0.001
Overall score	29.02±4.85	27.39±7.35	28.43±5.93	0.049

No preoperative baseline FSFI data were available. Results should be interpreted with caution and regarded as hypothesis-generating only
SD: Standard deviation, FSFI: Female sexual function index

evaluation at three months using the FSFI demonstrated significantly higher overall scores in the barbed suture group. In contrast, Einarsson et al. (16) found no significant differences in sexual function outcomes between barbed and conventional suture groups when assessed both pre- and post-operatively. These discrepancies highlight the need for prospective studies with baseline assessments to better understand the relationship between vault closure technique and sexual function.

Robotic surgery has become an integral component of contemporary gynecologic practice since the FDA approval of the da Vinci system in 2005 (3). Compared with conventional minimally invasive approaches, robotic platforms provide enhanced dexterity through seven degrees of freedom, surpassing the natural range of human hand movements (2). This improved maneuverability contributes to greater surgical precision, reduced surgeon fatigue, and improved operative efficiency. From a patient standpoint, robotic surgery is associated with less blood loss, reduced postoperative pain, shorter hospitalization, faster recovery, and improved cosmetic outcomes.

Study limitations

A key strength of this study is the precise measurement of suturing times using surgical video recordings rather than operative notes, enhancing the accuracy of intraoperative data. In addition, all procedures were performed by a single experienced surgeon proficient in both suturing techniques, minimizing inter-operator variability. The primary limitation remains the retrospective design, with reliance on medical records for perioperative and postoperative data. The retrospective design and surgeon-dependent choice of suture material introduce the possibility of selection bias. Although multivariable regression was used to adjust for measurable confounders, unmeasured variables may still influence outcomes. The imbalance in concomitant procedures between groups, particularly bilateral salpingo-oophorectomy, may have influenced operative outcomes. As procedure type was not included in the multivariable analysis, residual confounding remains possible. A key limitation of this study is the absence of preoperative FSFI assessment. Consequently, the observed postoperative differences in FSFI scores should be interpreted cautiously and cannot be conclusively linked to the type of suture used. Another important limitation of this study is the relatively short follow-up duration of three months. This limits the ability to evaluate longer-term outcomes, such as delayed vaginal cuff dehiscence, sustained vaginal cuff integrity, and long-term sexual function. Therefore, conclusions regarding safety and durability are restricted to the early postoperative period.

Conclusion

The findings of this study suggest that the use of unidirectional barbed sutures for vaginal vault closure during robotic hysterectomy was associated with shorter vault closure time, reduced duration of anesthesia, and a shorter hospital stay when compared with conventional Vicryl sutures. Barbed sutures may represent a feasible and time-efficient option for robotic vaginal vault closure. However, prospective randomized studies with longer follow-up and appropriate adjustment for confounders are required to confirm their safety, durability, and impact on functional outcomes.

Ethics

Ethics Committee Approval: *This retrospective study was conducted after approval from the Institutional Ethics Committee of All India Institute of Medical Sciences, Rishikesh (approval no.: AIIMS/IEC/19/1165; date: November 29, 2019).*

Informed Consent: *As all data were collected from existing records, the requirement for individual informed consent was waived by the committee, and all patient information was anonymized to ensure confidentiality.*

Footnotes

Author Contributions: *Surgical and Medical Practices: A.B., M.A., R.M., L.S., L.C., A.H., Concept: A.B., M.A., R.M., L.S., L.C., A.H., Design: A.B., M.A., R.M., L.S., L.C., A.H., Data Collection or Processing: M.A., L.S., A.H., Analysis or Interpretation: A.B., M.A., R.M., Literature Search: A.B., M.A., R.M., L.C., Writing: A.B., M.A., R.M., A.H.*

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References

1. Rout D, Sinha A, Palo SK, Kanungo S, Pati S. Prevalence and determinants of hysterectomy in India. Sci Rep. 2023; 13: 14569.
2. Probst P. A review of the role of robotics in surgery: to DaVinci and beyond! Mo Med. 2023; 120: 389-96.
3. George EI, Brand TC, LaPorta A, Marescaux J, Satava RM. Origins of robotic surgery: from skepticism to standard of care. JSLS. 2018; 22: e2018.00039.
4. Muaddi H, Hafid ME, Choi WJ, Lillie E, de Mestral C, Nathens A, et al. Clinical outcomes of robotic surgery compared to conventional surgical approaches (laparoscopic or open): a systematic overview of reviews. Ann Surg. 2021; 273: 467-73.

5. Moon AS, Garofalo J, Koirala P, Vu MT, Chuang L. Robotic surgery in gynecology. Surg Clin North Am. 2020; 100: 445-60.
6. Saget E, Peschot C, Bonin L, Belghiti J, Boulland E, Ghesquiere L, et al. Robot-assisted laparoscopy for deep infiltrating endometriosis: a retrospective French multicentric study (2008-2019) using the Society of European Robotic Gynecological Surgery endometriosis database. Arch Gynecol Obstet. 2022; 305: 1105-13.
7. Querleu D, Scambia G, Rychlik A. Reappraisal of robotic assistance in gynecologic oncology: the lessons of ROBOGYN-1004. Ann Surg Oncol. 2023; 30: 672-4.
8. Ala-Nissilä S, Laurikainen E, Mäkinen J, Jokimaa V. Vaginal cuff dehiscence is observed in a higher rate after total laparoscopic hysterectomy compared with other types of hysterectomy. Acta Obstet Gynecol Scand. 2019; 98: 44-50.
9. Eoh KJ, Lee YJ, Nam EJ, Jung HI, Kim YT. Clinical relevance of vaginal cuff dehiscence after minimally invasive versus open hysterectomy. J Clin Med. 2023; 12: 3001.
10. Zorzato PC, Vizza R, Garzon S, Bosco M, Festi A, Ricci A, et al. Incidence and prevention of vaginal cuff dehiscence after laparoscopic and robotic hysterectomy in benign conditions: an updated systematic review and meta-analysis. Medicina (Kaunas). 2025; 61: 647.
11. Jaime Moens B, Buonomo A, De Sutter P. Vaginal cuff dehiscence: two case reports and a review of the literature. J Clin Med. 2023; 12: 4187.
12. Uccella S, Zorzato PC, Kho RM. Incidence and prevention of vaginal cuff dehiscence after laparoscopic and robotic hysterectomy: a systematic review and meta-analysis. J Minim Invasive Gynecol. 2021; 28: 710-20.
13. Nichols P, Esposito A, Kolojeski M, Keomany J, Okut H, Morgan J, et al. Vaginal cuff dehiscence after robotic hysterectomy in endometrial cancer vs. non-cancer patients. Kans J Med. 2024; 17: 74-7.
14. Kim JH, Byun SW, Song JY, Kim YH, Lee HJ, Park TC, et al. Barbed versus conventional 2-layer continuous running sutures for laparoscopic vaginal cuff closure. Medicine (Baltimore). 2016; 95: e4981.
15. Ardovino M, Castaldi MA, Fraternali F, Ardovino I, Mosca L, Colacurci N, et al. Bidirectional barbed suture in total laparoscopic hysterectomy and lymph node dissection for endometrial cancer: technical evaluation and 1-year follow-up of 61 patients. J Laparoendosc Adv Surg Tech A. 2013; 23: 347-50.
16. Einarsson JI, Cohen SL, Gobern JM, Sandberg EM, Hill-Lydecker CI, Wang K, et al. Barbed versus standard suture: a randomized trial for laparoscopic vaginal cuff closure. J Minim Invasive Gynecol. 2013; 20: 492-8.
17. Smith K, Caceres A. Vaginal cuff closure in minimally invasive hysterectomy: a review of training, techniques, and materials. Cureus. 2017; 9: e1766.
18. Nawfal AK, Eisenstein D, Theoharis E, Dahlman M, Wegienka G. Vaginal cuff closure during robotic-assisted total laparoscopic hysterectomy: comparing vicryl to barbed sutures. JSLS. 2012; 16: 525-9.

Use of hormonal intrauterine device and quarterly injection for contraception in adolescents with mental disorders

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Abstract

Objective: To evaluate the continuity and satisfaction rate with contraceptive methods over 12 months in female adolescents with mental disorders (MD).

Material and Methods: Prospective cohort study carried out at a reference center for care for adolescents with MD. Adolescents with mild and moderate MD who opted for the hormonal intrauterine device (IUD) or a quarterly injectable contraceptive were included. Sociodemographic data were collected, such as age, education and gynecological data. Follow-up was quarterly for 12 months, with assessment of symptoms, desire to continue and satisfaction with the use of the quarterly injectable or hormonal IUD.

Results: One-hundred and three adolescents participated in the study, 34 (33%) of whom chose to use the hormonal IUD and 69 (67%) the quarterly injectable with depot medroxy-progesterone acetate (DMPA). After 12 months, 26 adolescents (76.5%) continued to use the IUD and 34 (49.3%) maintained the use of DMPA. During IUD follow-up, one teenager (2.9%) wanted to have it removed after three months, three (8.8%) developed spontaneous expulsion of the IUD and four (11.7%) were lost to follow-up. Regarding satisfaction after 12 months of use, of the 30 who maintained the method, 29 (96.6%) adolescents were satisfied. Among the 69 adolescents who chose to use DMPA, after 12 months of follow-up, 34 (50.7%) said they were satisfied. Among the 30 (44.7%) who discontinued use, the most frequent causes were irregular bleeding and weight gain. When comparing the two methods, a significant difference was demonstrated for IUD users in terms of continuity (p=0.0001), and satisfaction (p=0.00002).

Conclusion: Adolescents using the IUD exhibited significantly higher rate of continuity and reported greater satisfaction at 12 months compared to DMPA users. This result corroborates evidence of the preference for long-acting reversible methods for adolescents, especially for those who are most vulnerable. [J Turk Ger Gynecol Assoc. 2026; 27(3): 165-72]

Keywords: Adolescent, mental disorders, contraception, hormonal intrauterine device, depot medroxy-progesterone acetate, satisfaction

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Introduction

Teenage pregnancy is a complex phenomenon, which involves multiple dimensions of human life and is directly related to the sociocultural, economic and political context, as well as ethnic-racial and gender dimensions (1). In clinical practice, health professionals may encounter adolescents and young people with physical, intellectual and developmental disabilities in approximately 8.4% of consultations. For young people with physical and developmental disabilities, puberty and the

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beginning of menstruation can be accompanied by complaints such as abnormal bleeding, dysmenorrhea and premenstrual syndrome, in addition to difficulties with managing menstrual hygiene (2).

Pregnancy in adolescents with mental disorders (MD) occurs unintentionally almost all of the time. The presence of impulsivity, the lack of planning and behavioral control, added to the difficulty in regularly using contraceptives, makes this risk even greater (3). Furthermore, drug interactions may occur between hormonal contraceptives and some psychotropic drugs, which reduce the contraceptive effectiveness (4). The use of some of these medications during pregnancy may have a teratogenic effect, increasing the risk of prematurity and other fetal disorders (5).

Patients with MD may exhibit specific difficulties that increase the risk of failure or discontinuity in the use of contraceptive methods, such as dependence on another person to remember or the need for psychiatric hospitalization, which can lead to the interruption of contraceptive practice (6). Among the most used contraceptive methods in adolescents with MD are the quarterly injectable depot medroxy-progesterone acetate (DMPA), and long-acting reversible contraceptives (LARCs), such as hormonal and non-hormonal intrauterine devices (IUD) and subcutaneous implants (2). Surgical methods (sterilization) and the use of male condoms by the partner are also used (6).

LARCs are safe and appropriate contraceptive methods for most women and adolescents, including those with MD. Guidance suggests the use of these methods as the first choice for this population due to their high effectiveness, with failure rates of less than 1% per year. These contraceptives have the highest satisfaction and continuity rates among all reversible contraceptive methods (7). Currently, the literature has few studies regarding reproductive planning/contraception in this group (8). Therefore, this study sought to contribute to discussions about primary care for this population, helping to fill this knowledge gap.

The main objective of this study was to evaluate the continuity and satisfaction rate with the use of hormonal IUD and quarterly DMPA for 12 months in adolescents with MD.

Material and Methods

A prospective cohort study was carried out with adolescents with MD, followed for 12 months in a reference center for care for adolescents with MD, in Brasília, Federal District, DF, Brazil. Ethics committee approval was obtained from the Research Ethics Committee of UNIFESP - Hospital São Paulo - University Hospital, São Paulo, Brazil (approval no: 2.659.135; CEP/UNIFESP project no: 0286/2018; date: May 16, 2018). Adolescents with MD who were being monitored, who had started sexual activity, in need of contraception and who agreed to participate in the study were included. All the adolescents who participated had MD of mild to moderate intensity, including: depression; anxiety; bipolar mood disorder; mild to moderate cognitive impairment; obsessive-compulsive disorders; and others. The authorization of guardians and adolescents was carried out through the terms of consent and assent respectively. All adolescents participated in an information group about contraceptive methods and, in this way, were able to freely choose the method they preferred. Those who chose the hormonal IUD and the quarterly DMPA injectable were invited to participate in the study. An initial questionnaire was applied collecting sociodemographic and gynecological data at the reference center, as well as information regarding the MD and medications being used.

The hormonal IUD used was the one containing 52 mg of levonorgestrel. The IUD insertion in the adolescents occurred at the gynecology outpatient clinic by an experienced examiner, without the use of sedation or local anesthesia, in accordance with the manufacturer's technical recommendations. The adolescents were previously prepared for the insertion procedure and showed good tolerance to pain or discomfort. There were no difficulties or complications during the procedures. The quarterly injection with 150 mg of DMPA was administered every 3 months by the examiner, concomitantly with mental health follow-up consultations at the reference center.

Adolescents using both methods were instructed to return every 3 months for 12 months. At each consultation, symptoms, satisfaction and willingness to continue using the method were assessed using a follow-up questionnaire and simple and direct questions. Patient weight recording and gynecological examination were also carried out during follow-up. Previous data concerning continuity of use and satisfaction with the DMPA method have been published previously by our group (9).

Although cohort studies are a quantitative method, no specific previous studies were found on the use of these two contraceptive methods in an adolescent population with MD receiving outpatient care, which gives the research an exploratory character, which justifies the sample size.

Statistical analysis

Statistical analysis was performed using the SAS platform (Cary, NC, USA). Initially, descriptive analyses were applied to characterize the sample. Categorical variables were expressed as absolute and relative frequencies (n and %), while continuous variables were described using measures of central tendency (mean) and dispersion (standard deviation), according to the data distribution. The normality of continuous variables was verified using the Kolmogorov-Smirnov test.

For comparison between groups (IUD and injectable) regarding categorical variables, Pearson's chi-square test was used or, when necessary, Fisher's exact test. For continuous variables, Student's t-test for independent samples (in the case of normal distribution) or the Mann-Whitney U test (for non-parametric distributions) were used. The analysis of the continuity rate of contraceptive methods over 12 months was performed using the Kaplan-Meier survival analysis technique, with comparison between groups using the log-rank test. The significance level adopted was 5% ($p<0.05$).

Results

One hundred and three sexually active adolescents who needed some safe contraceptive methods were included in the study. Of these, 69 (67%) adolescents chose to use the DMPA and 34 (33%) the hormonal IUD. During the study, 30 (88%) of those who chose the hormonal IUD and 57 (82.6%) of those who chose DMPA used psychiatric medications.

The age of the 103 adolescents, when they started using the method, varied between 14 and 18 years old, with an average of 15.8 years old. Among the 69 DMPA users, the average age was 15.5 years and those who used hormonal IUD (n=34) was 16.5 years, which represents a significant difference between the two groups (p=0.02).

The average age at menarche of all adolescents was 11.6 years and that of sexual initiation was 14.2 years, and comparing the two groups, there was no difference for either variable (p=0.65 and p=0.19, respectively) (Table 1).

Among the data collected, we observed a high rate of academic delay (lag between year completed and age), represented by the low number of years of study. The two groups were similar in relation to this characteristic. Another notable fact was the high incidence of sexual violence in both groups, identified in 49.5% of all adolescents and similar between the two groups (p=0.17). Previous pregnancy in patients who chose the IUD was significantly higher (p=0.0001) than in patients who chose the DMPA (Table 1).

The most frequent MD in the studied population were depression 41 (39.8%), anxiety 19 (18.4%), intellectual disability 16 (15.5%), attention-deficit/hyperactivity disorder 14 (13.6%), bipolar affective disorder 13 (12.6%), and attempted self-extermination and self-mutilation 13 (12.6%). It is important to highlight that 73% of the adolescents had two or more psychiatric diagnoses, and their treatment included more than one type of psychiatric medication. Medications were used by 87 girls (85.4%), similarly between the two groups, with the most frequent medications being fluoxetine, valproic acid, methylphenidate, lithium, escitalopram and carbamazepine.

Table 1. Sociodemographic, gynecological, and mental disorder characteristics of adolescents using depot medroxyprogesterone acetate (DMPA) and hormonal intrauterine device (IUD)

Feature	Total 103		DMPA: 69		IUD: 34		Probability
	Mean	SD	Mean	SD	Mean	SD	p-value
Menarche (age)	11.6	1.46	11.3	1.18	11.1	0.23	0.659 (ST)
Sexual initiation (age)	14.2	1.65	13.8	0.18	13.6	0.32	0.1982(ST)
Start of use of the method (age)	15.8	1.10	15.5	0.1	16.5	0.2	0.0206(ST)
Feature	**Total: 103**		**DMPA: 69**		**IUD: 34**		**p-value**
	n (%)		**n (%)**		**n (%)**		
Education							
≤9 years of study	43 (40.2%)		31 (44.9%)		12 (35.2%)		0.9331(QS)
>9 to 12 years of study	60 (59.8%)		38 (55.1%)		22 (64.8%)		
Previous pregnancy							
None	89 (80.1%)		68 (98.5%)		21 (61.7%)		0.0001(EF)
One	14 (19.8%)		1 (1.5%)		13 (38.2%)		
Sexual violence							
Yes	51 (49.5%)		34 (49%)		17 (50%)		0.1716(QS)
No	51 (49%)		35 (51%)		16 (47%)		
Data ignored	1 (1.5%)		0 (0%)		1 (3%)		
Treatment of mental disorder							
Medicated	87 (85.4%)		57 (82.6%)		30 (88.3%)		0.8113(EF)
Psychotherapy only	16 (14.5%)		12 (17.4%)		4 (11.7%)		

ST: Student's t-test, QS: Chi-square test, EF: Exact of Fisher test, SD: Standard deviation

In the present study, adolescents presented significantly different bleeding patterns between the two groups. These differences were probably due to the higher rate of unfavorable bleeding (prolonged or frequent) in the group of DMPA users. Amenorrhea was recorded in 56.7% of the adolescents in both groups and changes in the bleeding pattern, such as amenorrhea and improvement in dysmenorrhea, were well accepted by the adolescents and their caregivers (Table 2).

The other side effect was weight gain, which occurred in a significantly higher proportion of DMPA users after 12 months (n=36; 53.7%), while in adolescents with hormonal IUD the gain was recorded in only 4 (11.7%) (Table 2). The average weight gain was 6.8 kg for the first group and 5.5 kg for the second. This was another reason that generated dissatisfaction and contraceptive cessation by many adolescents using DMPA.

After 12 months, of the 103 adolescents, 60 (62.6%) continued to use one of the methods (Table 3). Comparing continuation rates after this period, the number of adolescents who maintained the hormonal IUD was significantly higher than the number who continued to use DMPA. Only 1 (2.9%) of the group that opted for the hormonal IUD wanted to remove it after 3 months. Of this same group, 3 (8.7%) had their hormonal IUD expelled twice (they had a new attempt), and there was a loss to follow up of 4 adolescents (11.8%) who did not return for appointments. Regarding continued use of DMPA, 33 adolescents (47.8%) stopped using it and 2 (2.9%) abandoned the study.

In terms of user satisfaction after 12 months, of the 103 adolescents, 66 (64%) of them were satisfied (Table 3). Regarding the use of DMPA, approximately half of the adolescents (37=53.7%) were satisfied. Among those who stopped, the most common reasons for stopping were irregular bleeding and weight gain. With the use of the hormonal IUD, most of them (29=85.3%) were satisfied and, of these, 22 (64.7%) mentioned the desire to keep it for the duration of its validity (8 years) due to its convenience, reduction of dysmenorrhea and menstrual flow. The three adolescents who experienced early expulsions reported their satisfaction and their desire to maintain the method. Of the 34 who started the study, only one teenager reported dissatisfaction and wanted to withdraw before 3 months.

Discussion

Our data demonstrate a delay between start of sexual activity and the introduction of contraception use in this population. The average age of sexual initiation for the adolescents in the studied group was 14.2 years and the start of using contraceptive methods was after 1 to 2 years. The literature, similarly, also reports that adolescents with MD, despite undergoing many

Table 2. Characteristics of the bleeding pattern according to the classification of Belsey and weight changes after 12 months of use of depot medroxyprogesterone acetate (DMPA) and hormonal intrauterine device (IUD) and comparison between the two groups

Signs and symptoms	Total 97		DMPA 67		IUD 30		p-value
	n	%	n	%	n	%	
Bleeding pattern (chi-square test)							<0.0001[QS]
Amenorrhea	55	56.7	37	55.2	18	60	
Infrequent bleeding*	15	15.4	8	11.9	7	23.3	
Prolonged or frequent bleeding**	24	24.7	22	32.8	2	6.6	
Standard bleeding***	5	5.8	2	2.9	3	10	
Data unavailable	6	5.9	2	2.9	4	11.8	
Weight increase (exact of Fisher test)	**n**	**%**	**n**	**%**	**n**	**%**	<0.0001[EF]
Number of teenagers	40	41.2	36	53.7	4	13.3	
<2 kg	9	22.5	9	22.5	0	0	
From 2 to <5	11	27.5	8	20	2	5	
From 5 to <10 kg	12	30	11	27.5	1	2.5	
>10 kg	8	20	7	17.5	1	2.5	

[QS]: Chi-square test, [EF]: Exact of Fisher test
*Infrequent bleeding: 2 or fewer times in 90 days. **Prolonged or frequent bleeding: more than 5 times or lasting 14 days or more in 90 days. ***Standard bleeding: 3 to 5 times in 90 days (29)

Table 3. Continuity and satisfaction rates in the use of depot medroxy-progesterone acetate (DMPA) and hormonal intrauterine device (IUD) after 12 months of follow-up and comparison between the two groups

Continuity rate Kaplan-Meier test*							
Months of use of the method	**Total**		**DMPA**		**Hormonal IUD**		**Comparison**
	n	**%**	**n**	**%**	**n**	**%**	**p-value**
3	92	89.3	59	85.5	33	97.1	
6	85	82.4	57	82.6	28	82.3	0.000181(KM)
9	72	72.3	45	65.2	27	79.4	
>12	60	62.6	34	49.3	26	76.6	
Drop out***	6	7.45	2	2.9	4	12	
Satisfaction rate Fisher's exact test**							
	n	%	n	%	n	%	**p-value**
Satisfied	63	64.9	34	50.7	29	96.6	0.0000164(EF)
Dissatisfied	34	35	33	49.3	1	3.3	
Drop out***	6	6.1	2	2.9	4	11.7	

*Kaplan-Meier test (KM) was applied, with significance level adopted was 5% ($p<0.05$)
**Fisher's exact test (FE) was applied, which presented evidence that the satisfaction rates of both groups are different, with a significance of 99%, in favor of the group that opted for the hormonal IUD
***Adolescents who abandoned the study (drop out) were not considered in the satisfaction assessment

medical and psychological consultations, do not receive guidance on contraception (10,11).

The difference in the number of adolescents between the groups is mainly due to respect for the universal right to choose a contraceptive method granted to individuals. Several factors may have influenced the choice of method, such as lack of information, fear of IUD insertion, and the myth that it should not be used in women who have not been pregnant. This can be observed by the higher frequency of previous pregnancies (38.2%) among the teenagers who opted for the IUD, in addition to the higher average age in this group, which may be associated with a greater perception of risk and the need for a safe and long-lasting contraceptive method.

Considering the increased impulsivity and impairment of criticism, which frequently occur in a series of psychiatric disorders and neurological diseases, the reproductive risk is increased for this group of adolescents, often associated with some sexually transmitted disease (12,13). During the study there were no pregnancies, but five teenagers who stopped using the methods early became pregnant without planning. A Brazilian study with 255 women, including adolescents and adults with MD, found that 94.2% were not receiving specific medical attention about contraception. In this evaluation, 91% of women reported an active sexual life and among those who used some contraceptive method, 77.2% did it incorrectly (6). An American cohort study with 13,059 adult and adolescent women with intellectual or developmental disabilities, only 4.1% used LARCs and 29.8% used other moderately effective methods (14).

Women with MD present with specific problems that increase the risk of failure or discontinuity in the use of contraceptive methods (6). Therefore, contraceptive methods that do not require the woman's control are the most effective for them, with the most widely recommended being the hormonal IUD, subcutaneous implants and DMPA (2). DMPA has been indicated for women with MD due to its high efficacy, ease of dosing, improvement of dysmenorrhea and other symptoms (15). There is also a possible benefit in relation to the reduction of epileptic seizures (2). In this study, most adolescents opted for the quarterly injectable (67%).

Regarding the continued use of the methods, of the total of 69 adolescents who started using DMPA, only 49.3% of them maintained the use of the injectable for one year or more. This rate was also confirmed by adolescents without MD, participants in the CHOICE Project, where it was observed that among those who used DMPA for 12 months, the continuation rate was 47.3% (16). In our study, the most common reasons of early abandonment of this method among adolescents were menstrual irregularities (43.4% of adolescents) and weight gain (50.7%), similar to data observed in the literature (16-20).

The fact that half of the adolescents discontinued DMPA use impacted the study's results, which concluded, after 12 months of follow-up, that the number of participants in both groups was similar. These data support the recommendation of LARCs

as the first option for adolescents, especially those with mental health disorders.

According to other studies, weight gain may be more pronounced in women with pre-existing obesity/overweight before treatment initiation (21-24). The literature reports that women with MD using DMPA, when compared to those treated with non-hormonal contraceptives, may experience a greater increase in weight and body fat, which can be a major problem for those using psychotropic medications also associated with this effect (15). Logistic regression analysis was performed for the relationship between weight change and the medications used, but no significant differences were identified in our cohort.

Regarding bleeding patterns, a similar percentage was observed between the two methods, as well as the psychiatric medications used, which were similar in both groups. The report of depression, present in both groups, was evaluated by the mental health team and was not directly related to the use of contraceptive methods, but rather to the pre-existing psychiatric condition.

The incidence of amenorrhea among adolescents who used DMPA in this study was 54%, considered a positive effect by both them and their caregivers, due to the difficulties in managing menstrual hygiene. The literature points to different results, as it shows that among adolescent users with special needs, DMPA suppresses menstruation and provides effective contraception, leading to amenorrhea in up to 90% of women after the fourth dose (12 months) (2). The incidence rate of amenorrhea among adolescents who used the hormonal IUD was similar (52.9%). Studies investigating its use in adolescents with developmental disabilities have reported amenorrhea rates of up to 70% and low rates of expulsion and removal due to bleeding or pain (2). On the other hand, a study over 5 years, with 300 adolescents with intellectual disabilities and an average age of 12.1 years, reported a gradual decrease in the use of DMPA, which went from 59% to 17.8%, while there was an increase in the use of hormonal IUD, increasing from 2.8% to 19.2% (25).

Considering the presence of MD and the average age of the participants (16.1 years), the 76.6% rate of continuity of use in 12 months of hormonal IUD use in this study can be evaluated as good. A similar result was found in a recent systematic review with women and adolescents without other diseases (26). In another study, published in 2020, which evaluated the use of hormonal IUD in 159 nulliparous patients with physical, intellectual or developmental disabilities, a high rate of continuity (95%) of the method within 1 year was also reported. In this study, it was noteworthy that the majority of insertion procedures (96%) were performed in a surgical center (27). Some studies reported that one of the disadvantages of using hormonal IUD is their cost and the need for hospitalization for insertion, with general anesthesia (25,27). However, in the present study, the insertion was carried out in an outpatient clinic and without sedation, which appears to be a major difference. During or after insertion of the hormonal IUD, there were no complications or mention of severe pain by the patients. Outpatient insertion minimizes costs and makes this method much more accessible, even facilitating logistics for the healthcare team, family and caregivers. It is possible that reassurance prior to insertion, in a simple and understandable way for the adolescents who opted for this method, in addition to the environment, which was the gynecology outpatient clinic with which they were already familiar, contributed to facilitating the process. In any case, it is important to highlight that training professionals for the correct and safe insertion of the device is necessary to care for this population.

The results of this study with adolescents with MD demonstrated higher rates of continuity of contraceptive use and satisfaction among hormonal IUD users. This result is in line with the data presented by a study carried out with women with bipolar disorder, which compared the rates of continuity, complications and psychiatric hospitalizations between the methods used. The authors reported that women with an IUD (TCu 380-A, 86%; hormonal IUD, 87%) had a continuation rate of use 31% ($p<0.0001$) higher than those who opted for the quarterly injectable. Furthermore, no differences were observed in the number of hospitalizations for bipolar disorder or depression between the contraceptive groups evaluated (28).

The data from the present study corroborate those in the literature, in which a hormonal IUD is considered as the first option for adolescents with MD due to its effective, comfortable, safe, long-term contraception and good bleeding control. There were no limitations to its use related to drug interactions and the multiple comorbidities frequently associated with it, such as endocrine and metabolic diseases, obesity, attention and cognitive deficits, factors that make the use of other contraceptive methods difficult.

Considering depot DMPA, which, despite the widely proven adverse consequences in the literature, has been widely used for decades, in contrast to the various benefits and few adverse effects of the hormonal IUD, there is a perceived need to make this technology available for reproductive planning in the public health system, especially in vulnerable populations.

Based on our results, and considering those existing in the literature, a protocol proposal will be developed so that the hormonal IUD can be offered to the adolescent population with MDs in the public health system, when there is a need or risk of unplanned pregnancy. Given the lack of recognition of their needs by health professionals and reproductive planning services, we realize the importance (and urgency) of expanding care, including information on the sexual and reproductive

specificities of these adolescents. In addition, expanding access to modern contraceptive methods, in cases where safe, reversible and long-lasting contraception is indicated and can benefit many people with MDs, as well as their families and society should also be promoted.

Offering the IUD among the available contraceptive options and incorporating practical strategies into care, such as careful explanations about the method, as well as about the IUD insertion procedure, combined with good follow-up of adolescents, will allow for better adherence to contraceptive use and acceptance of the discomfort of outpatient insertion. Furthermore, routine counseling and resolution of potential adverse events may increase continuation rates and satisfaction among adolescents who are new users of LARC methods.

Study limitations

This study has limitations in relation to the fact that some adolescents with MD may have difficulties expressing themselves and understanding which contraceptive method is most appropriate for them. This fact could explain the higher discontinuation rate after 12 months.

Another limitation was the difficulty in evaluating outcomes by subgroup of MDs, mainly due to the fact that most adolescents had two or more psychiatric diagnoses, and their treatment included more than one type of psychiatric medication.

The limitations for replicating this experience in the public health system, both in services that serve adolescents with MDs and in Basic Health Units, lie in the unavailability of the hormonal IUD for insertion as a contraceptive option for this vulnerable population.

Conclusion

There was a notable delay in the introduction of the use of contraception after start of sexual activity for the population of adolescents with MD, which demonstrated a lack of specific attention in terms of reproductive planning for this group. Considering the features of female adolescents with MD and the greater difficulty in using contraceptive methods, we concluded that there was a good rate of continuity and satisfaction after 12 months with the use of the hormonal IUD compared to the use of the quarterly injectable. The presence of irregular bleeding and weight gain were the most common causes of abandonment of the injectable method.

Ethics

Ethics Committee Approval: *Ethics committee approval was obtained from the Research Ethics Committee of UNIFESP - Hospital São Paulo - University Hospital, São Paulo, Brazil (approval no: 2.659.135; CEP/UNIFESP project no: 0286/2018; date: May 16, 2018).*

Informed Consent: *All participants signed the consent form.*

Footnotes

Author Contributions: *Surgical and Medical Practices: G.S.S.C., Concept: C.A.F.G., Design: C.A.F.G., Data Collection or Processing: G.S.S.C., M.R.T., Analysis or Interpretation: M.R.T., Literature Search: E.A.J., Writing: E.A.J.*

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References

1. Diretrizes Intersetoriais para Garantia de Direitos Sexuais e Direitos Reprodutivos, Prevenção e Atenção Integral à Gravidez de Adolescentes no Município de São Paulo. Plano de Impacto Coletivo da edição 2017-2020 da Plataforma dos Centros Urbanos, uma iniciativa do Fundo das Nações Unidas para a Infância (UNICEF) com a Prefeitura de São Paulo. São Paulo, dezembro de 2020. Available from: https://drive.prefeitura.sp.gov.br/cidade/secretarias/upload/saude/anexo4_diretriz_intersetoriais_gravidez_adolescentes2020.pdf. Assssed Feb 02 2026.
2. Dural Ö, Taş İS, Akhan SE. Management of menstrual and gynecologic concerns in girls with special needs. J Clin Res Pediatr Endocrinol. 2020; 12(Suppl 1): 41-5.
3. Liu Z, Sun L, Yang R, Cui S, Yao G, Liu Y, et al. Teenage pregnancy: focus on people with mental disorders. Front Psychiatry. 2024; 15: 1305572.
4. Toffol E, Partonen T, Heikinheimo O, But A, Latvala A, Haukka J. Associations between use of psychotropic medications and use of hormonal contraception among girls and women aged 15-49 years in Finland: a nationwide, register-based, matched case-control study. BMJ Open. 2022; 12: e053837.
5. Fabiano N, Wong S, Gupta A, Tran J, Bhambra N, Min KK, et al. Safety of psychotropic medications in pregnancy: an umbrella review. Mol Psychiatry. 2025; 30: 327-35.
6. Bello JK, Salas J, Meyer D, Heiden-Rootes K, Davis DM, Keegan Garrett E, et al. Mental health diagnoses and early removal of long-acting reversible contraception. J Affect Disord. 2020; 262: 333-6.
7. ACOG committee opinion no. 735: adolescents and long-acting reversible contraception: implants and intrauterine devices. Obstet Gynecol. 2018; 131: e130-9.
8. Mental health of adolescents. World Health Organization. 2024. Available from: https://www.who.int/news-room/fact-sheets/detail/adolescent-mental-health
9. Cezimbra GSS, Araujo Júnior E, Guazzelli CAF. Contraception in adolescents with mental disorders: adherence and satisfaction in the use of depot medroxyprogesterone acetate. Rev Bras Ginecol Obstet. 2025; 47: e-rbgo9.
10. Horner-Johnson W, Moe EL, Stoner RC, Klein KA, Edelman AB, Eden KB, et al. Contraceptive knowledge and use among women with intellectual, physical, or sensory disabilities: a systematic review. Disabil Health J. 2019; 12: 139-54.
11. Matin BK, Ballan M, Darabi F, Karyani AK, Soofi M, Soltani S. Sexual health concerns in women with intellectual disabilities: a systematic review in qualitative studies. BMC Public Health. 2021; 21: 1965.

12. Karle A, Agardh A, Larsson M, Arunda MO. Risky sexual behavior and self-rated mental health among young adults in Skåne, Sweden - a cross-sectional study. BMC Public Health. 2023; 23: 9.
13. Crisp ZC, Grant JE. Impulsivity across psychiatric disorders in young adults. Compr Psychiatry. 2024; 130: 152449.
14. Wu J, Zhang J, Mitra M, Parish SL, Minama Reddy GK. Provision of moderately and highly effective reversible contraception to insured women with intellectual and developmental disabilities. Obstet Gynecol. 2018; 132: 565-74.
15. McCloskey LR, Wisner KL, Cattan MK, Betcher HK, Stika CS, Kiley JW. Contraception for women with psychiatric disorders. Am J Psychiatry. 2021; 178: 247-55.
16. Madden T, Barker AR, Huntzberry K, Secura GM, Peipert JF, McBride TD. Medicaid savings from the Contraceptive CHOICE Project: a cost-savings analysis. Am J Obstet Gynecol. 2018; 219: 595.e1-595.e11.
17. Durante JC, Sims J, Jarin J, Gold MA, Messiah SE, Francis JKR. Long-acting reversible contraception for adolescents: a review of practices to support better communication, counseling, and adherence. Adolesc Health Med Ther. 2023; 14: 97-114.
18. Todd N, Black A. Contraception for adolescents. J Clin Res Pediatr Endocrinol. 2020; 12: 28-40.
19. Lopez LM, Ramesh S, Chen M, Edelman A, Otterness C, Trussell J, et al. Progestin-only contraceptives: effects on weight. Cochrane Database Syst Rev. 2016; 2016: CD008815.
20. Mitchell L, Vellanki B, Tang L, Hunter K, Finnegan A, Swartz JJ, et al. Contraceptive provision to women with intellectual and developmental disabilities enrolled in medicaid. Obstet Gynecol. 2023; 142: 1477-85.
21. Patel RR, Sheth PN, Mehta AS. Depot medroxyprogesterone acetate injection as contraceptive method. Int J Reprod Contracept Obstet Gynecol. 2024; 13: 2030-5.
22. American College of Obstetricians and Gynecologists' Committee on Adolescent Health Care. Committee Opinion No. 668: menstrual manipulation for adolescents with physical and developmental disabilities. Obstet Gynecol. 2016; 128: e20-5.
23. Sims J, Lutz E, Wallace K, Kassahun-Yimer W, Ngwudike C, Shwayder J. Depo-medroxyprogesterone acetate, weight gain and amenorrhea among obese adolescent and adult women. Eur J Contracept Reprod Health Care. 2020; 25: 54-9.
24. Batt CE, Sheeder J, Love-Osborne K. Weight gain patterns in adolescent and young adult women with the etonogestrel implant: comparison by weight category. J Adolesc Health. 2021; 69: 815-23.
25. Kirkham YA, Allen L, Kives S, Caccia N, Spitzer RF, Ornstein MP. Trends in menstrual concerns and suppression in adolescents with developmental disabilities. J Adolesc Health. 2013; 53: 407-12.
26. Zgliczynska M, Kocaj K, Szymusik I, Dutsch-Wicherek MM, Ciebiera M, Kosinska-Kaczynska K. Levonorgestrel-releasing intrauterine system as a contraceptive method in nulliparous women: a systematic review. J Clin Med. 2020; 9: 2101.
27. Schwartz BI, Alexander M, Breech LL. Intrauterine device use in adolescents with disabilities. Pediatrics. 2020; 146: e20200016.
28. Berenson AB, Asem H, Tan A, Wilkinson GS. Continuation rates and complications of intrauterine contraception in women diagnosed with bipolar disorder. Obstet Gynecol. 2011; 118: 1331-6.

Prognostic significance of lymphovascular space invasion in endometrial cancer and its relationship with other prognostic factors

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Abstract

Objective: To investigate the prognostic significance of lymphovascular space invasion (LVSI) and its relationship with other prognostic factors in patients with endometrial cancer.

Material and Methods: Patients with stage 1a/1b endometrial cancer who underwent hysterectomy and/or staging surgery between January 2016 and December 2020 at a tertiary referral center were retrospectively analyzed. Pathological data including histological type, stage, grade, LVSI (lymphatic invasion, vascular invasion), tumor size, depth of myometrial invasion, cervical involvement, lymph node evaluation (pelvic, paraaortic), and peritoneal wash cytology were analyzed using univariate and multivariate methods.

Results: The study included 304 patients. Non-endometrioid tumors were associated with a 6.35-fold higher risk of LVSI. Each 1 mm increase in tumor size raised the risk by 1.03-fold. LVSI was present in 53.3% of cases with lymph node metastasis and was 7.2-fold more frequent in deceased patients (odds ratio: 7.209; 95% confidence interval: 3.137-16.570; $p<0.001$). Multivariate analysis identified tumor grade and survival as independent predictors of LVSI: grade 3 tumors had a 4.88-fold higher risk ($p=0.014$), and mortality was associated with a 4.16-fold higher risk ($p=0.007$). Survival was significantly linked to LVSI, tumor size ≥35 mm, and recurrence, but not to age, histological type, lymph node status, or peritoneal cytology.

Conclusion: Our results demonstrated that LVSI was significantly associated with histological grade and survival. Furthermore, LVSI, tumor diameter ≥35 mm, and recurrence were found to significantly affect survival, highlighting their prognostic relevance for risk assessment and postoperative management. [J Turk Ger Gynecol Assoc. 2026; 27(3): 173-86]

Keywords: Endometrial cancer, lymphovascular space invasion, prognostic factors

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Introduction

Endometrioid carcinoma is the most common type of uterine malignancy, with abnormal uterine bleeding as the main symptom. Unopposed estrogen exposure is a key factor in its development (1). Risk factors include nulliparity, late onset of menopause, obesity, polycystic ovary syndrome, diabetes, estrogen-secreting tumors, estrogen therapy without progesterone supplementation during menopause, tamoxifen use, and Lynch II syndrome (2).

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Prognostic factors in endometrial cancer guiding surgery include histological type, grade, tumor size, myometrial invasion depth, cervical involvement, peritoneal fluid cytology, lymphovascular space invasion (LVSI), and lymph node metastasis (3).

LVSI is typically defined as the presence of tumor cells in endothelial-lined channels outside the primary uterine tumor, though its precise definition is still debated (4). LVSI has been demonstrated in several studies as an independent adverse prognostic factor for recurrence and survival (5-7). Tumor spread to vascular and lymphatic spaces is believed to enhance metastasis to pelvic and paraaortic lymph nodes, indicating a more aggressive disease course (7,8).

The aim of this study was to determine the prognostic significance of LVSI in endometrial cancer and evaluate its relationship with other prognostic factors.

Material and Methods

This study includes endometrial cancer cases (stage 1a-4b) who underwent hysterectomy and/or staging surgery at a tertiary referral center between January 1st, 2016, and December 31st, 2020. Retrospective data were collected from patient files and electronic records. Pathological data, including histological type, stage, grade, LVSI, tumor size, myometrial invasion depth, cervical involvement, lymph node evaluation, and peritoneal fluid cytology, were analyzed according to the 2009 FIGO criteria. Uterine sarcoma cases, those with synchronous primary tumors, and those without LVSI data were excluded.

LVSI was defined as tumor cells or cell clusters attached to the walls of lymphatic and vascular vessels within sections that included both the tumor and surrounding healthy tissue. Tissue samples obtained from the material were transferred to paraffin blocks for LVSI detection. Sections were then cut from these blocks, mounted on slides, and stained with hematoxylin and eosin (H&E). The presence of LVSI was initially examined on H&E-stained slides (Leica Biosystems) containing sections that included both the tumor and surrounding healthy tissue. Subsequently, for slides suspicious of LVSI, new sections were taken from the blocks and stained immunohistochemically using the Leica Bond Max device. In these immunohistochemical analyses, podoplanin (D2-40, Cell Marque) was used to identify lymphatic structures, and CD34 (QBEnd/10, Leica Biosystems), CD31 (1A10, Leica Biosystems), and Factor 8 (von Willebrand factor, 36B11, Leica Biosystems) were used to identify vascular structures.

For stage 1 endometrioid-type endometrial cancer, primary surgery included total abdominal hysterectomy (TAH) + bilateral salpingo-oophorectomy (BSO) ± peritoneal fluid sampling ± lymphadenectomy. Staging surgery was performed if any of the following criteria were met based on frozen section results:

- Non-endometrioid tumor type;
- Tumor grade ≥2;
- Myometrial invasion depth ≥½;
- Tumor size >2 cm;
- Cervical invasion.

Staging surgery included TAH + BSO + bilateral pelvic and paraaortic lymph node dissection + omental sampling + peritoneal fluid sampling. Peritoneal cytology was not evaluated by pathology in some patients with stage 1 low-grade diagnosis (stage 1a/1b, grade 1). All cases were reviewed in a multidisciplinary tumor board (gynecology, medical oncology, pathology, radiology), and adjuvant treatment indications (chemotherapy, radiotherapy, or both) were determined based on postoperative final pathological results and directed to the appropriate departments.

Ethics committee approval

This study was approved by the İstanbul Medeniyet University, Göztepe Training and Research Hospital, Clinical Research Ethics Committee (approval number: 2021/0529, date: 27.10.2021).

Data analysis

The data were analyzed using IBM SPSS Statistics version 18 (IBM Inc, Armonk, NY, USA). The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Categorical variables are expressed as frequencies (n) and percentages (%). Continuous variables meeting the assumptions for parametric tests are presented as mean ± standard deviation (SD), while those not meeting the assumptions are presented as median (minimum and maximum) values. For the analysis of categorical variables, Pearson's chi-square test, Fisher's exact test, or the Fisher-Freeman-Halton exact test were applied, and Yates' continuity correction and post-hoc Bonferroni adjustment were performed as necessary. For comparing the medians between two groups, the Mann-Whitney U test was used, as parametric assumptions were not met. Univariate and multivariate logistic regression analyses were employed to identify independent risk factors associated with dependent variables, and variables with $p<0.02$ in univariate analyses were included in the multivariate model. The results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). Survival probabilities were estimated using the Kaplan-Meier method, and the log-rank test was conducted to assess differences in survival probabilities across variable levels. Cox regression analysis was performed to identify factors influencing survival. A significance level of 0.05 was considered statistically significant for all analyses.

Results

The mean ± SD age of the 304 patients included in the study was 61.52±10.27 years. The youngest patient was 28 years old, and the oldest was 90 years old. The age distribution of the patients is shown in Figure 1.

The analysis of histological features is presented in Table 1.

Upon analysis of the cases, the most common histological type was endometrioid carcinoma, accounting for 84.5% (n=257), while non-endometrioid histological types accounted for 15.5% (n=47).

The distribution of cases based on invasion areas is presented in Table 2.

Lymphatic invasion was observed in 36 patients (11.8%), vascular invasion in 30 patients (9.9%), and LVSI (involving lymphatic, vascular, or both) in 50 patients (16.4%), as seen in Table 2.

The relationship between lymphatic invasion in patients and independent variables was analyzed, and the results are shown in Table 3.

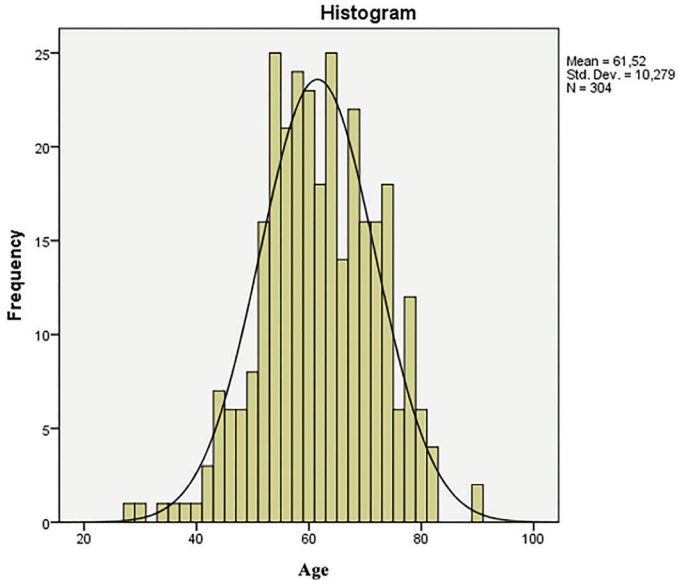

Figure 1. Age distribution histogram of the patients

Table 1. Histological features

Histological features (n=304)	n	%
Endometrioid	257	84.5
Serous	17	5.6
Dedifferentiated endometrioid	12	3.9
Clear cell	8	2.6
Mixed	4	1.3
Undifferentiated endometrioid	3	1.0
Mucinous	2	0.7
Serous papillary	1	0.3

Lymphatic invasion was present in 8.2% of endometrioid tumors but was significantly more common in non-endometrioid tumors at 31.9% (p<0.001). The rates of lymphatic invasion were 5.5% in stage 1, 13.0% in stage 2, 51.6% in stage 3, and 30.8% in stage 4, with significant differences observed across stages (p<0.001). Further analysis revealed that lymphatic invasion was significantly lower in stage 1 compared to stages 3 and 4, while stage 3 had a significantly higher rate than stages 1 and 2. A significant difference was also observed based on grade, with lymphatic invasion in grade 3 being notably higher at 30.3%. In our series, lymph node metastasis occurred in 53.3% of patients with lymphatic invasion. The invasion rate was 47.1% in those with pelvic-only metastasis and 87.5% in those with both pelvic and paraaortic metastasis, significantly higher than in patients without metastatic lymph nodes or those not undergoing lymphadenectomy (p<0.001). Cervical stromal invasion was found in 50 patients, with 43 having stromal invasion. Lymphatic invasion was seen in 27.9% of these patients, compared to 9.1% in those without cervical involvement (p=0.002). Tumor size was larger in patients with lymphatic invasion (median 45 mm) compared to those without it (median 32 mm), a statistically significant difference (p<0.001).

Survival analysis showed that 9.4% of surviving patients had lymphatic invasion, while 37.0% of deceased patients had lymphatic invasion (p<0.001). No significant associations were found between lymphatic invasion and age (p=0.813), positive peritoneal wash fluid (p=0.130), or recurrence (p=0.194).

The relationship between vascular invasion and independent variables was analyzed, and the results are shown in Table 4.

Vascular invasion was found in 6.2% of endometrioid tumors and 29.8% of non-endometrioid tumors (p<0.001). The rates of vascular invasion were 3.0% in stage 1, 21.7% in stage 2, 38.7% in stage 3, and 46.2% in stage 4, with significant differences across stages (p<0.001). Further analysis showed that vascular invasion was significantly lower in stage 1 compared to stages 3 and 4. Vascular invasion was also higher in grade 3 (31.8%) than in grade 1 (1.8%) and grade 2 (5.5%) (p<0.001).

Table 2. Invasion features

Variables (n=304)	n	%
Lymphatic invasion		
No	268	88.2
Yes	36	11.8
Vascular invasion		
No	274	90.1
Yes	30	9.9
Lymphovascular invasion		
No	254	83.6
Yes	50	16.4

Table 3. Relationship between lymphatic invasion and independent variables

Variable (n=304)	Lymphatic invasion		p-value
	No (n=268)	Yes (n=36)	
Age (years)	61.57±10.40	61.14±9.42	0.813
Histological type			
Endometrioid	236 (91.8)	21 (8.2)	**<0.001**
Non-endometrioid	32 (68.1)	15 (31.9)	
Stage			
1[a]	224 (94.5)	13 (5.5)	**<0.001**
2[a,b]	20 (87.0)	3 (13.0)	
3[c]	15 (48.4)	16 (51.6)	
4[b,c]	9 (69.2)	4 (30.8)	
Grade			
1[a]	107 (97.3)	3 (2.7)	**<0.001**
2[a]	115 (89.8)	13 (10.2)	
3[b]	46 (69.7)	20 (30.3)	
Lymph node metastasis			
No lymphadenectomy[a]	116 (95.9)	5 (4.1)	**<0.001**
No[a]	138 (90.2)	15 (9.8)	
Yes[b]	14 (46.7)	16 (53.3)	
Metastatic lymph node location			
No lymphadenectomy[a]	116 (95.9)	5 (4.1)	**<0.001**
No[a]	138 (90.2)	15 (9.8)	
Pelvic region only[b]	9 (52.9)	8 (47.1)	
Paraaortic region only[a,b]	4 (80.0)	1 (20.0)	
Both regions[b]	1 (12.5)	7 (87.5)	
Cervical involvement			
No[a]	231 (90.9)	23 (9.1)	**0.002**
Superficial invasion[a,b]	6 (85.7)	1 (14.3)	
Stromal invasion[b]	31 (72.1)	12 (27.9)	
Cytology			
Not evaluated**	145 (90.6)	15 (9.4)	0.130
Benign	119 (86.2)	19 (13.8)	
Malignant	4 (66.7)	2 (33.3)	
Tumor size (mm)	32 (1-125)	45 (12-130)	**<0.001**
Number of pelvic lymph nodes removed	8 (0-60)	21 (0-54)	**<0.001**
Number of paraaortic lymph nodes	0 (0-42)	5 (0-74)	**<0.001**
Follow-up time (months)	35 (1-69)	35 (2-60)	0.579
Recurrence			
No	251 (89.0)	31 (11.0)	0.194
Yes	17 (77.3)	5 (22.7)	
Survival			
Alive	251 (90.6)	26 (9.4)	**<0.001**
Deceased	17 (63.0)	10 (37.0)	

Results are presented as mean ± standard deviation, median (minimum-maximum), or n (% of total row). Statistical tests used: Student's t-test, Mann-Whitney U test, Pearson's chi-square test, Fisher's exact test, Fisher-Freeman-Halton exact test. Differences between groups are indicated with lowercase letters

**Peritoneal cytology was not evaluated by pathology in some stage 1 low-grade patients (stage 1a/1b, grade 1)

Table 4. Relationship between vascular invasion and independent variables

Variable (n=304)	Vascular invasion		p-value
	No (n=274)	Yes (n=30)	
Age (years)	61.30±10.45	63.57±8.40	0.251
Histological type			
Endometrioid	241 (93.8)	16 (6.2)	**<0.001**
Non-endometrioid	33 (70.2)	14 (29.8)	
Stage			
1[a]	230 (97.0)	7 (3.0)	**<0.001**
2[a,b]	18 (78.3)	5 (21.7)	
3[c]	19 (61.3)	12 (38.7)	
4[b,c]	7 (53.8)	6 (46.2)	
Grade			
1[a]	108 (98.2)	2 (1.8)	**<0.001**
2[a]	121 (94.5)	7 (5.5)	
3[b]	45 (68.2)	21 (31.8)	
Lymph node metastasis			
No Lymphadenectomy[a]	115 (95.0)	6 (5.0)	**<0.001**
No[a]	140 (91.5)	13 (8.5)	
Yes[b]	19 (63.3)	11 (36.7)	
Metastatic lymph node location			
No lymphadenectomy[a]	115 (95.0)	6 (5.0)	**<0.001**
No[a]	140 (91.5)	13 (8.5)	
Pelvic region only[b]	14 (82.4)	3 (17.6)	
Paraaortic region only[a,b]	3 (60.0)	2 (40.0)	
Both regions[b]	2 (25.0)	6 (75.0)	
Cervical involvement			
No[a]	241 (94.9)	13 (5.1)	**<0.001**
Superficial invasion[a,b]	5 (71.4)	2 (28.6)	
Stromal invasion[b]	28 (65.1)	15 (34.9)	
Cytology			
Not evaluated**	146 (91.2)	14 (8.8)	0.489
Benign	123 (89.1)	15 (10.9)	
Malignant	5 (83.3)	1 (16.7)	
Tumor size (mm)	32 (1-125)	57.5 (25-130)	**<0.001**
Number of pelvic lymph nodes removed	9 (0-60)	16 (0-54)	0.104
Number of paraaortic lymph nodes	0 (0-42)	3 (0-74)	**0.001**
Follow-up time (months)	35.5 (1-69)	25 (1-60)	**0.017**
Recurrence			
No	257 (91.1)	25 (8.9)	0.084
Yes	17 (77.3)	5 (22.7)	
Survival			
Alive	258 (93.1)	19 (6.9)	**<0.001**
Deceased	16 (59.3)	11 (40.7)	

Results are presented as mean ± standard deviation, median (minimum-maximum), or n (% of total row). Statistical tests used: Student's t-test, Mann-Whitney U test, Pearson's chi-square test, Fisher's exact test, Fisher-Freeman-Halton exact test. Differences between groups are indicated with lowercase letters

**Peritoneal cytology was not evaluated by pathology in some stage 1 low-grade patients (stage 1a/1b, grade 1)

In patients with lymph node metastasis (36.7%), vascular invasion was notably higher than in those without metastasis (8.5%) or who did not undergo lymphadenectomy (5.0%) (p<0.001). In cases with metastasis in the paraaortic region or both pelvic and paraaortic regions, the rate of vascular invasion was significantly higher than in patients who did not undergo lymphadenectomy (p<0.001). In patients with cervical stromal (34.9%) or superficial involvement (28.6%), the rate of vascular invasion was significantly higher compared to those without cervical involvement (5.1%) (p<0.001). The median tumor size in patients with vascular invasion was 57.5 mm, compared to 32 mm in those without (p<0.001). The median number of paraaortic lymph nodes removed was 3 in patients with vascular invasion, compared to 0 in those without (p=0.001). The median follow-up duration was 25 months for patients with vascular invasion and 35.5 months for those without (p=0.017). Survival analysis showed 6.9% of survivors had vascular invasion, while 40.7% of deceased patients did (p<0.001).

The relationship between the presence of LVSI and independent variables was analyzed, with results presented in Table 5.

LVSI was significantly less common in endometrioid tumors compared to dedifferentiated, undifferentiated endometrioid, and serous tumors (p<0.001). LVSI rates were 7.6% in stage 1, 30.4% in stage 2, 58.1% in stage 3, and 53.8% in stage 4, with significant differences across stages (p<0.001). Further analysis showed that LVSI was significantly less common in stage 1 compared to other stages. In grade 3, LVSI (43.9%) was significantly more common than in grade 1 (4.5%) and grade 2 (12.5%) (p<0.001).

In patients with lymph node metastasis (60.0%), LVSI was significantly more frequent than in those without lymph node metastasis (15.0%) or those who did not undergo lymphadenectomy (7.4%) (p<0.001). LVSI rates were also higher in patients with pelvic-only or combined pelvic and paraaortic metastasis compared to those without metastasis. LVSI rate was 46.5% in patients with cervical stromal involvement, compared to 11.0% in those without cervical involvement (p<0.001). In addition, LVSI rates were significantly higher in patients with myometrial invasion of ½ or more, compared to those with no or less than ½ myometrial invasion (p<0.001).

Table 5. Relationship between LVSI presence and independent variables

Variables (n=304)	LVSI		p-value
	No (n=254)	Yes (n=50)	
Age (years)	61.38±10.41	62.24±9.60	0.589
Histological features			
Endometrioid[a]	228 (88.7)	29 (11.3)	**<0.001**
Dedifferentiated endometrioid[b]	5 (41.7)	7 (58.3)	
Undifferentiated endometrioid[b]	0 (0.0)	3 (100.0)	
Serous[b]	10 (58.8)	7 (41.2)	
Clear cell[a,b]	6 (75.0)	2 (25.0)	
Mucinous[a,b]	2 (100.0)	0 (0.0)	
Papillary serous[a,b]	0 (0.0)	1 (100.0)	
Mixed[a,b]	3 (75.0)	1 (25.0)	
Stage			
1[a]	219 (92.4)	18 (7.6)	**<0.001**
2[b]	16 (69.6)	7 (30.4)	
3[b]	13 (41.9)	18 (58.1)	
4[b]	6 (46.2)	7 (53.8)	
Grade			
1[a]	105 (95.5)	5 (4.5)	**<0.001**
2[a]	112 (87.5)	16 (12.5)	
3[b]	37 (56.1)	29 (43.9)	
Lymph node metastasis			
No lymphadenectomy[a]	112 (92.6)	9 (7.4)	**<0.001**
No[a]	130 (85.0)	23 (15.0)	
Yes[b]	12 (40.0)	18 (60.0)	

Table 5. Continued

Variables (n=304)	LVSI		p-value
	No (n=254)	Yes (n=50)	
Metastatic lymph node location			
No lymphadenectomy[a]	112 (92.6)	9 (7.4)	**<0.001**
No[a]	130 (85.0)	23 (15.0)	
Pelvic region only[b]	8 (47.1)	9 (52.9)	
Paraaortic region only[a,b]	3 (60.0)	2 (40.0)	
Both regions[b]	1 (12.5)	7 (87.5)	
Cervical involvement			
No[a]	226 (89.0)	28 (11.0)	**<0.001**
Superficial invasion[a,b]	5 (71.4)	2 (28.6)	
Stromal invasion[b]	23 (53.5)	20 (46.5)	
Myometrial invasion			
No invasion[a]	27 (100.0)	0 (0.0)	**<0.001**
<1/2[a]	148 (95.5)	7 (4.5)	
≥1/2[b]	79 (64.8)	43 (35.2)	
Cytology			
Not evaluated**	138 (86.2)	22 (13.8)	0.188
Benign	112 (81.2)	26 (18.8)	
Malignant	4 (66.7)	2 (33.3)	
Tumor size (mm)	30 (1-125)	46 (12-130)	**<0.001**
Number of pelvic lymph nodes removed	8 (0-60)	19.5 (0-54)	**0.002**
Number of paraaortic lymph nodes	0 (0-42)	3.5 (0-74)	**<0.001**
Follow-up time (months)	35.5 (1-69)	30.5 (1-60)	**0.029**
Recurrence			
No	239 (84.8)	43 (15.2)	0.085
Yes	15 (68.2)	7 (31.8)	
Survival			
Alive	241 (87.0)	36 (13.0)	**<0.001**
Deceased	13 (48.1)	14 (51.9)	

Results are presented as mean ± standard deviation, median (minimum-maximum), or n (% of total row). Statistical tests used: Student's t-test, Mann-Whitney U test, Pearson's chi-square test, Fisher's exact test, Fisher-Freeman-Halton exact test. Differences between groups are indicated with lowercase letters
**Peritoneal cytology was not evaluated by pathology in some stage 1 low-grade patients (stage 1a/1b, grade 1)
LVSI: Lymphovascular space invasion

The median tumor size was 46 mm (12-130) in patients with LVSI and 30 mm (1-125) in those without LVSI (p<0.001). The median number of pelvic lymph nodes removed was 19.5 (0-54) in patients with LVSI and 8 (0-60) in those without (p=0.002). The median number of paraaortic lymph nodes removed was 3.5 (0-74) in patients with LVSI and 0 (0-42) in those without (p<0.001). Follow-up duration was shorter for patients with LVSI (p=0.029). When comparing survival outcomes according to LVSI status, LVSI was detected in 13.0% of surviving patients and in 51.9% of deceased patients, with the rate of LVSI being significantly higher in deceased patients (p<0.001). No significant differences were found between LVSI occurrence and age (p=0.589), abdominal wash fluid positivity (p=0.188), or recurrence (p=0.085) (Table 5).

The factors affecting the presence of LVSI were analyzed using logistic regression, and the results are shown in Table 6.

The risk of LVSI was 6.35 times higher in non-endometrioid tumors. When tumor stages were considered, the risk of LVSI was 5.32 times higher in stage 2 tumors, 16.84 times higher in stage 3 tumors, and 14.19 times higher in stage 4 tumors compared to stage 1 tumors (p<0.05).

The risk of LVSI was 3.00 times higher in grade 2 tumors and 16.45 times higher in grade 3 tumors compared to grade 1 tumors (p<0.05). There was no significant change in LVSI risk in patients with superficial cervical invasion (p=0.173), but it was 7.01 times higher in patients with cervical stromal invasion [OR: 7.019; 95% CI: 3.429-14.368; p<0.001]. Each 1-mm increase in tumor size was found to increase the

Table 6. Factors affecting the presence of lymphovascular space invasion-findings of univariate and multivariate logistic regression analysis

	Univariate		Multivariate	
Variable	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Histological type				
Endometrioid	Reference	-	Reference	-
Non-endometrioid	6.350 (3.176-12.696)	**<0.001**	1.637 (0.538-4.982)	0.386
Stage				
1	Reference	-	Reference	-
2	5.323 (1.939-14.613)	**0.001**	0.625 (0.095-4.122)	0.625
3	16.846 (7.128-39.816)	**<0.001**	3.260 (0.915-11.612)	0.068
4	14.194 (4.311-46.734)	**<0.001**	1.700 (0.316-9.158)	0.537
Grade				
1	Reference	-	Reference	-
2	3.000 (1.062-8.478)	0.038	1.854 (0.603-5.700)	0.281
3	16.459 (5.933-45.662)	**<0.001**	4.886 (1.385-17.233)	**0.014**
Cervical involvement				
No	Reference	-	Reference	-
Superficial invasion	3.229 (0.598-17.431)	0.173	0.625 (0.042-9.236)	0.732
Stromal invasion	7.019 (3.429-14.368)	**<0.001**	3.027 (0.744-12.319)	0.122
Tumor size (mm)	1.038 (1.024-1.053)	**<0.001**	1.016 (0.996-1.035)	0.116
Survival				
Alive	Reference	-	Reference	-
Deceased	7.209 (3.137-16.570)	**<0.001**	4.160 (1.470-11.774)	**0.007**

CI: Confidence interval, OR: Odds ratio

likelihood of LVSI by 1.03 times [OR: 1.038; 95% CI: (1.024-1.053); p<0.001]. In survival analysis, LVSI was 7.20 times more common in deceased patients compared to those who survived [OR: 7.209; 95% CI: (3.137-16.570); p<0.001]. The multivariate analysis revealed that grade and survival were significantly associated with LVSI. LVSI was found to be 4.88 times more common in grade 3 patients compared to grade 1 patients [OR: 4.886; 95% CI: (1.385-17.233); p=0.014] and 4.16 times more common in deceased patients compared to survivors [OR: 4.160; 95% CI: (1.470-11.774); p=0.007].

The relationship between the patients' survival status and independent variables was analyzed, and the findings are shown in Table 7.

Stage 1 patients had a significantly lower mortality rate (5.1%) compared to Stage 2 (21.7%) and Stage 4 (38.5%) (p<0.001). Similarly, Grade 3 tumors showed higher mortality (22.7%) than Grade 1 (3.6%) and Grade 2 (6.2%) (p<0.001). Patients with both pelvic and para-aortic lymph node metastases had higher mortality than those without lymphadenectomy (p=0.036). Although cervical stromal invasion was initially associated with survival, this was not confirmed in multivariate analysis. Median tumor size was significantly larger in deceased patients (46 mm) than in survivors (33 mm) (p<0.001). Mortality was also higher among patients with recurrence (40.9%) compared to those without (6.4%) (p<0.001). No significant associations were found between overall survival and histological type (p=0.064), lymph node metastasis (p=0.137), or positive peritoneal cytology (p=0.795) (Table 7).

Survival analyses based on the general clinical characteristics of the patients are presented in Table 8.

The overall survival time of patients was 63.16 months. Patients aged 60 years and below had significantly longer survival times than those over 60 years (64.94 vs. 60.50 months; p=0.016). Survival was longer for endometrioid tumors (64.38 months) compared to non-endometrioid tumors (52.28 months; p=0.020). Survival times by stage were 65.87 months for stage 1, 53.42 months for stage 2, 49.86 months for stage 3, and 42.99 months for stage 4 (p<0.001). For grade, survival was 65.79 months for grade 1, 65.23 months for grade 2, and 48.50 months for grade 3 (p<0.001). Patients with lymphatic, vascular, or lymphovascular invasion had significantly shorter survival times compared to those without (p<0.001 for all).

Table 7. Relationship between overall survival and independent variables

Variable (n=304)	Survival		p-value
	Alive (n=277)	Deceased (n=27)	
Age (years)	61.11±10.32	65.70±8.94	**0.026**
Histological type			
Endometrioid	238 (92.6)	19 (7.4)	0.064
Non-endometrioid	39 (83.0)	8 (17.0)	
Stage			
1[a]	225 (94.9)	12 (5.1)	**<0.001**
2[b]	18 (78.3)	5 (21.7)	
3[a,b]	26 (83.9)	5 (16.1)	
4[b]	8 (61.5)	5 (38.5)	
Grade			
1[a]	106 (96.4)	4 (3.6)	**<0.001**
2[a]	120 (93.8)	8 (6.2)	
3[b]	51 (77.3)	15 (22.7)	
Lymph node metastasis			
No lymphadenectomy	115 (95.0)	6 (5.0)	0.137
None	136 (88.9)	17 (11.1)	
Present	26 (86.7)	4 (13.3)	
Site of metastatic lymph node			
No lymphadenectomy[a]	115 (95.0)	6 (5.0)	**0.036**
None[a,b]	136 (88.9)	17 (11.1)	
Pelvic only[a,b]	16 (94.1)	1 (5.9)	
Para-aortic only[a,b]	5 (100.0)	0 (0.0)	
Both regions[b]	5 (62.5)	3 (37.5)	
Cervical involvement			
None[a]	236 (92.9)	18 (7.1)	**0.027**
Superficial invasion[a]	5 (71.4)	2 (28.6)	
Stromal invasion[a]	36 (83.7)	7 (16.3)	
Cytology			
Not evaluated**	146 (91.2)	14 (8.8)	0.795
Benign	126 (91.3)	12 (8.7)	
Malignant	5 (83.3)	1 (16.7)	
Tumor size (mm)	33 (1-130)	46 (10-120)	**<0.001**
Number of pelvic lymph nodes removed	9 (0-60)	25 (0-57)	**0.004**
Number of paraaortic lymph nodes	0 (0-74)	5 (0-35)	**0.001**
Follow-up time (months)	36 (10-69)	20 (1-60)	**<0.001**
Recurrence			
No	264 (93.6)	18 (6.4)	**<0.001**
Yes	13 (59.1)	9 (40.9)	

Results are presented as mean ± standard deviation, median (minimum-maximum), or n (% of total row). Statistical tests used: Student's t-test, Mann-Whitney U test, Pearson's chi-square test, Fisher's exact test, Fisher-Freeman-Halton exact test. Differences between groups are indicated with lowercase letters

**Peritoneal cytology was not evaluated by pathology in some stage 1 low-grade patients (stage 1a/1b, grade 1)

Tumor size ≤35 mm was associated with longer survival (65.78 months) compared to tumors >35 mm (58.73 months; p<0.001). Recurrence significantly reduced survival, with 64.68 months for patients without recurrence and 32.80 months for those with recurrence (p<0.001) (Figure 2, Table 8).

A univariate and multivariate Cox regression analysis was performed to identify factors affecting survival in patients (Table 9).

The analysis revealed that patients over 60 years had a 2.76 times higher mortality risk compared to those aged 60 years and below (OR: 2.767; 95% CI: 1.169-6.550; p=0.021). Non-endometrioid tumors had a 2.58 times higher mortality risk than endometrioid tumors (OR: 2.583; 95% CI: 1.130-5.906; p=0.025). Mortality rates for stage 2, 3, and 4 tumors were 5.25, 3.50, and 9.51 times higher, respectively, than for stage 1 tumors (p<0.05). Grade 3 tumors had an 8.75 times higher mortality rate than grade 1 tumors (p<0.001). Lymphatic invasion (OR: 4.574), vascular invasion (OR: 8.114), LVSI (OR: 6.525), tumor size >35 mm (OR: 4.560), and recurrence (OR: 9.965) were all significantly associated with higher mortality (p<0.001 for all). In multivariate analysis,

Table 8. Survival analysis based on general clinical features of patients

	Mean survival (months)	Standard error	95% CL lower limit	95% CL upper limit	p-value
Overall survival	63.16	1.08	61.03	65.29	-
Age (years)					
≤60 years	64.94	1.12	62.74	67.14	**0.016**
>60 years	60.50	1.82	56.93	64.08	
Histological type					
Endometrioid	64.38	1.01	62.39	66.37	**0.020**
Non-endometrioid	52.28	2.86	46.68	57.89	
Stage					
1	65.87	0.87	64.15	67.59	**<0.001**
2	53.42	4.91	43.78	63.05	
3	49.86	2.88	44.21	55.51	
4	42.99	7.73	27.83	58.14	
Grade					
1	65.79	1.07	63.69	67.90	**<0.001**
2	65.23	1.28	62.70	67.75	
3	48.50	2.77	43.05	53.94	
Lymphatic invasion					
No	65.01	0.93	63.18	66.84	**<0.001**
Yes	48.16	3.58	41.13	55.18	
Vascular invasion					
No	65.39	0.87	63.68	67.10	**<0.001**
Yes	42.45	4.64	33.34	51.56	
Lymphovascular invasion					
No	65.80	0.86	64.12	67.49	**<0.001**
Yes	46.74	3.24	40.39	53.10	
Tumor size (mm)					
≤35 mm	65.78	0.88	64.04	67.52	**<0.001**
>35 mm	58.73	2.09	54.64	62.83	
Recurrence					
No	64.68	0.99	62.73	66.64	**<0.001**
Yes	32.80	3.76	25.41	40.19	

CL: Confidence limit

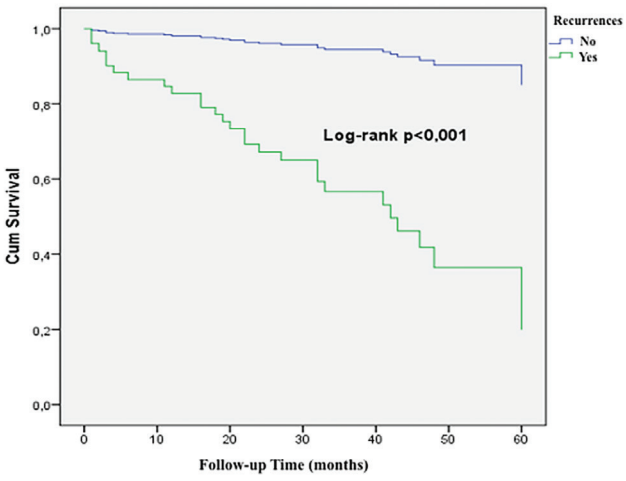

Figure 2. Survival according to recurrence status-Kaplan-Meier, Log-rank test

recurrence remained a significant predictor of higher mortality (OR: 8.100; p<0.001). Other factors showed no significant relationship with survival (p>0.05) (Table 9).

Discussion

Prognostic factors in endometrial cancer have been extensively debated, and it has been demonstrated that these factors can influence success of treatment strategies. Recent studies have identified key prognostic indicators, including poor histological differentiation, older age, deep myometrial invasion, non-endometrioid histology, lymph node involvement, LVSI, lower uterine segment involvement, and molecular markers, as the main factors assessed in predicting the development of recurrence.

Age is commonly recognized as an independent prognostic factor. In a study by Veade et al. (9) the average age of patients without LVSI was 63.2 years, while those with LVSI had an

Table 9. Factors affecting survival-univariate and multivariate Cox regression analysis results

	Univariate		Multivariate	
Variables	**OR (95% CL)**	**p**	**OR (95% CL)**	**p**
Age (years)				
≤60 years	1	-	1	-
>60 years	2.767 (1.169-6.550)	**0.021**	2.512 (0.937-6.734)	0.067
Histological type				
Endometrioid	1	-	1	-
Non-endometrioid	2.583 (1.130-5.906)	**0.025**	0.336 (0.103-1.101)	0.072
Stage				
1	1	-	1	-
2	5.256 (1.847-14.958)	**0.002**	1.918 (0.527-6.982)	0.323
3	3.508 (1.230-9.999)	**0.019**	1.549 (0.412-5.826)	0.518
4	9.515 (3.345-27.067)	**<0.001**	3.463 (0.824-14.562)	0.090
Grade				
1	1	-	1	-
2	1.817 (0.546-6.042)	0.330	1.360 (0.385-4.803)	0.633
3	8.751 (2.885-26.541)	**<0.001**	2.735 (0.681-10.987)	0.156
Lymphatic invasion				
No	1	-	1	-
Yes	4.574 (2.093-9.996)	**<0.001**	0.772 (0.169-3.519)	0.738
Vascular invasion				
No	1	-	1	-
Yes	8.114 (3.758-17.517)	**<0.001**	1.850 (0.388-8.813)	0.440
Lymphovascular invasion				
No	1	-	1	-
Yes	6.525 (3.061-13.909)	<0.001	3.829 (0.509-28.808)	0.192
Tumor size (mm)				
≤35 mm	1	-	1	-
>35 mm	4.560 (1.837-11.319)	**0.001**	1.441 (0.459-4.525)	0.531
Recurrence				
No	1	-	1	-
Yes	9.965 (4.368-22.736)	**<0.001**	8.100 (2.967-22.116)	**<0.001**

OR: Odds ratio, CL: Confidence limit

average age of 64.8 years. In our study, the mean age of patients without LVSI was 61.38±10.41 years, and 62.24±9.60 years for those with LVSI, with no significant association found between LVSI and age (p=0.589). Furthermore, patients over 60 years had a 2.76 times higher mortality risk, consistent with existing literature.

In our study, while LVSI was observed in 11.3% of endometrioid tumors, the rate of LVSI in endometrioid carcinoma was found to be significantly lower than that in non-endometrioid histological type carcinomas. In non-endometrioid tumors, LVSI was 6.35 times more common. In a study conducted by Hahn et al. (10), similar to our findings, LVSI was more frequently detected in non-endometrioid tumors, and LVSI was present in 37.2% of patients with endometrioid adenocarcinoma.

Myometrial invasion is one of the prognostic factors that alters staging and significantly impacts survival. In our study, 27 patients (8.9%) had no myometrial invasion, while 122 patients (40.1%) had invasion of ½ or more. The rate of LVSI was significantly higher in patients with deeper myometrial invasion. Dane and Bakir (11) found that myometrial invasion depth was the most significant prognostic factor and correlated with pelvic lymph node metastasis, cervical involvement, and LVSI in 122 endometrial cancer cases. A meta-analysis by Wang et al. (12) analyzing 28,904 patients, also found a connection between myometrial invasion depth and LVSI, with a higher risk in patients with invasion of ½ or more.

In our study, the LVSI rate was 46.5% in patients with cervical stromal invasion, compared to 11% in those without cervical involvement, with cervical stromal invasion increasing the likelihood of LVSI by 7.01 times. A study of 671 stage 1 and stage 3 endometrial cancer patients also found a higher incidence of LVSI in those with cervical stromal invasion (13). Similarly, Koskas et al. (14) reported a correlation between LVSI and cervical stromal invasion in 485 stage 1 and 2 endometrial cancer patients.

In terms of tumor stage, 59.5% of cases were stage 1a, 18.4% were stage 1b, and 77.9% were stage 1. LVSI rates were lower in stage 1 patients. Stage 2 had 5.32-fold higher rates of LVSI, stage 3 had 16.84-fold increase times more, and stage 4 had 14.19-fold greater rate of LVSI than stage 1. Similarly, Stålberg et al. (15) reported more advanced stages in LVSI-positive patients. Peters et al. (16) found that increased LVSI in both stage 1-2 and stage 3-4 patients was associated with decreased survival. In the present study and consistent with the literature, the survival time of patients with LVSI was shorter than those without LVSI. Moreover, the mortality rate was 7.20 times higher in the presence of LVSI.

There is a strong relationship between histological grade and prognosis in endometrial cancer. In the present study, as the grade increased, the incidence of LVSI also increased. Furthermore, the mortality rate was 8.75-times higher in grade 3 tumors compared to grade 1 tumors. However, when examining survival times and contrary to the literature, survival was similar in grade 1 and grade 2 tumors, while survival was significantly reduced in grade 3 tumors. Similarly, in the study by Berchuck et al. (17) it was reported that survival decreased with the presence of high-grade histology.

Canlorbe et al. (18) showed that low-risk endometrial cancer cases with tumors ≥35 mm have lower rates of recurrence-free survival. Similarly, patients with tumors ≤35 mm in our cohort had longer survival. A study by Çakır et al. (19) reported a 5-year survival rate of 94% in patients with tumors ≤35 mm, compared to 89% in those with tumors >35 mm, and found tumor size was not a recurrence risk factor. Guo et al. (20) demonstrated that, as tumor size increases, the risk of lymph node metastasis and recurrence also rises, with a prognostic cut-off for metastasis and recurrence at 42.5 mm. In our study, the median tumor size was 45 mm in patients with LVSI and 32 mm in those without LVSI. Tumors with vascular invasion had a median size of 57.5 mm, compared to 32 mm in those without vascular invasion. A 1-unit increase in tumor size increased the likelihood of LVSI by 1.03 times. Laufer et al. (21) also reported a significant relationship between LVSI and tumors >20 mm.

Fotopoulou et al. (22) identified LVSI and grade as key prognostic factors for lymph node metastasis, while Briët et al. (23) similarly reported that LVSI increased the likelihood of pelvic lymph node metastasis in stage 1 patients. In our study, lymph node metastasis occurred in 53.3% of LVSI-positive patients, with rates of 47.1% in pelvic-only and 87.5% in combined pelvic and para-aortic metastasis. Consistent with Visser et al. (24) and Wakayama et al. (25), vascular invasion was associated with higher recurrence, while LVSI correlated with lymph node metastasis. Neal et al. (26) further noted LVSI as a significant prognostic factor, even in node-negative patients, and Jorge et al. (27) reported a 3- to 10-fold increased risk of nodal metastasis with LVSI. Although LVSI was significant in univariate analysis, its loss of significance in the multivariable Cox regression model may be explained by collinearity with established prognostic factors and the limited events-per-variable ratio.

We found no relationship between LVSI and positive peritoneal lavage fluid. In the study by Takenaka et al. (28) which included 1,616 endometrial cancer cases, positive peritoneal cytology was reported as a poor prognostic factor across all stages and tumor types. A 2016 meta-analysis by Lee et al. (29) also concluded that positive peritoneal cytology reduced 5-year overall survival, but like our study, found no correlation between LVSI and positive peritoneal cytology. Furthermore, we found no relationship between positive peritoneal lavage fluid and overall survival, in contrast to several earlier studies.

Based on current TCGA and ProMisE classifications, the prognostic significance of LVSI varies across molecular subtypes in endometrial cancer. While LVSI has been consistently reported as an important risk factor in the "no specific molecular profile" (NSMP) and mismatch repair deficiency (MMRd) tumors, its prognostic relevance appears attenuated in POLE-mutant cases. In the present study, LVSI was significantly associated with advanced stage, higher tumor grade, lymph node metastasis, and adverse survival outcomes, findings that are broadly consistent with previously reported prognostic patterns, particularly within the NSMP/MMRd subgroups. These results suggest that LVSI reflects underlying biological heterogeneity and may provide complementary prognostic information, even in the absence of molecular classification (30,31).

In our cohort, lymphatic invasion, vascular invasion, tumor size >35 mm, and recurrence were significantly associated with survival, in line with the existing literature. In contrast, no significant association was observed between survival and tumor histological type, lymph node metastasis, or positive peritoneal lavage cytology. Histological grade emerged as a strong determinant of both LVSI and survival outcomes. Importantly, this study contributes population-specific data by evaluating the prevalence and prognostic impact of LVSI in a Turkish endometrial cancer cohort, which remains underrepresented in molecular prognostic studies.

Study limitations

The limitations of this study include its uni-centric, retrospective design, reliance on archival data, and incomplete access to certain patient records. Nevertheless, its single-center nature and relatively large sample size provide a homogeneous dataset, strengthening the internal validity of the findings.

Clinical implications

Given the association between LVSI and adverse outcomes, patients with LVSI-positive tumors may benefit from closer postoperative follow-up. In selected cases, LVSI status could also be considered when individualizing adjuvant treatment decisions.

Conclusion

LVSI was strongly associated with tumor grade and survival in patients with endometrial cancer. Tumor size ≥35 mm and recurrence emerged as independent prognostic factors, underscoring their relevance for postoperative management. In addition, LVSI was significantly associated with lymph node metastasis and mortality, reinforcing its role as a marker of aggressive disease biology. Collectively, these findings support the integration of LVSI and tumor burden into postoperative risk stratification and treatment planning. The findings are largely consistent with prior studies and add meaningful value to both regional and international literature by presenting a large, population-based cohort from Türkiye. Further prospective studies incorporating molecular stratification are warranted to validate and extend these results.

Ethics

Ethics Committee Approval: *This study was approved by the İstanbul Medeniyet University, Göztepe Training and Research Hospital, Clinical Research Ethics Committee (approval number: 2021/0529, date: 27.10.2021).*

Informed Consent: *Retrospective data were collected from patient files and electronic records.*

Footnotes

Author Contributions: *Surgical and Medical Practices: A.K., M.K., Concept: A.K., Design: V.N.G., Data Collection or Processing: V.N.G., Analysis or Interpretation: A.K., M.K., Literature Search: V.N.G., Writing: V.N.G.*

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References

1. Morice P, Leary A, Creutzberg C, Abu-Rustum N, Darai E. Endometrial cancer. Lancet. 2016; 387: 1094-108.
2. Feinberg J, Albright B, Black J, Lu L, Passarelli R, Gysler S, Whicker M, et al. Ten-year comparison study of type 1 and 2 endometrial cancers: risk factors and outcomes. Gynecol Obstet Invest. 2019; 84: 290-7.
3. Uharček P. Prognostic factors in endometrial carcinoma. J Obstet Gynaecol Res. 2008; 34: 776-83.
4. Stålberg K, Bjurberg M, Borgfeldt C, Carlson J, Dahm-Kähler P, Flöter-Rådestad A, et al. Lymphovascular space invasion as a predictive factor for lymph node metastases and survival in endometrioid endometrial cancer - a Swedish Gynecologic Cancer Group (SweGCG) study. Acta Oncol. 2019; 58: 1628-33.
5. Kondalsamy-Chennakesavan S, Yu C, Kattan MW, Leung Y, Sykes P, Nascimento M, et al. Nomograms to predict isolated loco-regional or distant recurrence among women with uterine cancer. Gynecol Oncol. 2012; 125: 520-5.
6. Aristizabal P, Graesslin O, Barranger E, Clavel-Chapelon F, Haddad B, Luton D, et al. A suggested modification to FIGO stage I endometrial cancer. Gynecol Oncol. 2014; 133: 192-6.
7. Mariani A, Keeney GL, Aletti G, Webb MJ, Haddock MG, Podratz KC. Endometrial carcinoma: paraaortic dissemination. Gynecol Oncol. 2004; 92: 833-8.
8. Sato M, Taguchi A, Fukui Y, Kawata A, Taguchi S, Kashiyama T, et al. Blood vessel invasion is a strong predictor of postoperative recurrence in endometrial cancer. Int J Gynecol Cancer. 2018; 28: 875-81.

9. Veade AE, Foote J, Ehrisman J, Broadwater G, Davidson BA, Lee PS, et al. Associations between lymphovascular space invasion, nodal recurrence, and survival in patients with surgical stage I endometrioid endometrial adenocarcinoma. World J Surg Oncol. 2019; 17: 80.
10. Hahn HS, Lee IH, Kim TJ, Lee KH, Shim JU, Kim JW, et al. Lymphovascular space invasion is highly associated with lymph node metastasis and recurrence in endometrial cancer. Aust N Z J Obstet Gynaecol. 2013; 53: 293-7.
11. Dane C, Bakir S. The effect of myometrial invasion on prognostic factors and survival analysis in endometrial carcinoma. Afr Health Sci. 2019; 19: 3235-41.
12. Wang J, Xu P, Yang X, Yu Q, Xu X, Zou G, et al. Association of myometrial invasion with lymphovascular space invasion, lymph node metastasis, recurrence, and overall survival in endometrial cancer: a meta-analysis of 79 studies with 68,870 patients. Front Oncol. 2021; 11: 762329.
13. Matsuo K, Garcia-Sayre J, Medeiros F, Casabar JK, Machida H, Moeini A, et al. Impact of depth and extent of lymphovascular space invasion on lymph node metastasis and recurrence patterns in endometrial cancer. J Surg Oncol. 2015; 112: 669-76.
14. Koskas M, Bassot K, Graesslin O, Aristizabal P, Barranger E, Clavel-Chapelon F, et al. Impact of lymphovascular space invasion on a nomogram for predicting lymph node metastasis in endometrial cancer. Gynecol Oncol. 2013; 129: 292-7.
15. Stålberg K, Kjølhede P, Bjurberg M, Borgfeldt C, Dahm-Kähler P, Falconer H, et al. Risk factors for lymph node metastases in women with endometrial cancer: a population-based, nation-wide register study-on behalf of the Swedish Gynecological Cancer Group. Int J Cancer. 2017; 140: 2693-700.
16. Peters EEM, Léon-Castillo A, Hogdall E, Boennelycke M, Smit VTHBM, Hogdall C, et al. Substantial lymphovascular space invasion is an adverse prognostic factor in high-risk endometrial cancer. Int J Gynecol Pathol. 2022; 41: 227-34.
17. Berchuck A, Anspach C, Evans AC, Soper JT, Rodriguez GC, Dodge R, et al. Postsurgical surveillance of patients with FIGO stage I/II endometrial adenocarcinoma. Gynecol Oncol. 1995; 59: 20-4.
18. Canlorbe G, Bendifallah S, Laas E, Raimond E, Graesslin O, Hudry D, et al. Tumor size, an additional prognostic factor to include in low-risk endometrial cancer: results of a french multicenter study. Ann Surg Oncol. 2016; 23: 171-7.
19. Çakır C, Kılıç İÇ, Yüksel D, Karyal YA, Üreyen I, Boyraz G, et al. Does tumor size have prognostic value in patients undergoing lymphadenectomy in endometrioid-type endometrial cancer confined to the uterine corpus? Turk J Med Sci. 2019; 49: 1403-10.
20. Guo CM, Dai YB, Geng J, Li H, Dong YY, Wang ZQ, et al. [Correlation between the primary tumor size of endometrial carcinoma and lymph node metastasis and recurrence]. Zhonghua Fu Chan Ke Za Zhi. 2021; 56: 264-70. [Chinese].
21. Laufer J, Scasso S, Papadia A, Sosa C, Cirillo F, Raspagliesi F. Association between tumor diameter and lymphovascular space invasion among women with early-stage endometrial cancer. Int J Gynaecol Obstet. 2013; 123: 142-5.
22. Fotopoulou C, Savvatis K, Kraetschell R, Schefold JC, Lichtenegger W, Sehouli J. Systematic pelvic and aortic lymphadenectomy in intermediate and high-risk endometrial cancer: lymph-node mapping and identification of predictive factors for lymph-node status. Eur J Obstet Gynecol Reprod Biol. 2010; 149: 199-203.
23. Briët JM, Hollema H, Reesink N, Aalders JG, Mourits MJ, ten Hoor KA, et al. Lymphvascular space involvement: an independent prognostic factor in endometrial cancer. Gynecol Oncol. 2005; 96: 799-804.
24. Visser NCM, Werner HMJ, Krakstad C, Mauland KK, Trovik J, Massuger LFAG, et al. Type of vascular invasion in association with progress of endometrial cancer. APMIS. 2017; 125: 1084-91.
25. Wakayama A, Kudaka W, Matsumoto H, Aoyama H, Ooyama T, Taira Y, et al. Lymphatic vessel involvement is predictive for lymph node metastasis and an important prognostic factor in endometrial cancer. Int J Clin Oncol. 2018; 23: 532-8.
26. Neal SA, Graybill WS, Garrett-Mayer E, McDowell ML, McLean VE, Watson CH, et al. Lymphovascular space invasion in uterine corpus cancer: what is its prognostic significance in the absence of lymph node metastases? Gynecol Oncol. 2016; 142: 278-82.
27. Jorge S, Hou JY, Tergas AI, Burke WM, Huang Y, Hu JC, et al. Magnitude of risk for nodal metastasis associated with lymphvascular space invasion for endometrial cancer. Gynecol Oncol. 2016; 140: 387-93.
28. Takenaka M, Kamii M, Iida Y, Yanaihara N, Suzuki J, Takahashi K, et al. Re-thinking the prognostic significance of positive peritoneal cytology in endometrial cancer. Gynecol Oncol. 2021; 161: 135-42.
29. Lee B, Suh DH, Kim K, No JH, Kim YB. Influence of positive peritoneal cytology on prognostic factors and survival in early-stage endometrial cancer: a systematic review and meta-analysis. Jpn J Clin Oncol. 2016; 46: 711-7.
30. Berek JS, Matias-Guiu X, Creutzberg C, Fotopoulou C, Gaffney D, Kehoe S, et al. FIGO staging of endometrial cancer: 2023. Int J Gynaecol Obstet. 2023; 162: 383-94.
31. León-Castillo A, de Boer SM, Powell ME, Mileshkin LR, Mackay HJ, Leary A, et al. Molecular classification of the PORTEC-3 trial for high-risk endometrial cancer: impact on prognosis and benefit from adjuvant therapy. J Clin Oncol. 2020; 38: 3388-97.

Maternal and neonatal outcomes following cesarean myomectomy: a comparison between fibroid-associated and fibroid-free cesarean deliveries

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Abstract

Objective: To compare maternal and neonatal outcomes among women undergoing cesarean section (CS) with concomitant myomectomy, women with uterine fibroids managed conservatively at cesarean delivery, and women without uterine fibroids.

Material and Methods: This retrospective cohort study included women who delivered by CS between May 2017 and December 2024. Patients were classified into three groups: CS with myomectomy (Group 1), CS with fibroids without myomectomy (Group 2), and CS without fibroids (Group 3). Maternal outcomes included perioperative changes in hemoglobin, hematocrit, and platelet counts, transfusion requirement, and length of hospital stay. Neonatal outcomes included birth weight, birth length, and Apgar scores. Appropriate parametric and non-parametric statistical tests were used for group comparisons.

Results: The study cohort numbered 682 with 252 (36.95%), 178 (26.1%) and 252 (36.95%) women in Groups 1, 2 and 3, respectively. Postoperative hemoglobin, hematocrit, and platelet levels differed significantly among the three groups (all $p<0.05$). However, hemoglobin deficit did not differ significantly between Group 1 and Group 2 ($p=0.346$), while both groups showed greater hemoglobin deficit than Group 3 ($p<0.05$). Transfusion rates and hospitalization duration differed significantly between groups ($p<0.05$), with longer hospital stay observed in transfused patients regardless of group. Maximum myoma volume was higher in Group 1, whereas myoma count was greater in Group 2 and total myoma volume was comparable between these groups ($p=0.09$). Neonatal birth weight was significantly lower in Group 2 compared with Groups 1 and 3 ($p<0.05$), while no difference was observed between Groups 1 and 3 ($p=0.956$). Other neonatal outcomes were similar.

Conclusion: Cesarean myomectomy was associated with larger changes in hematologic parameters and transfusion rates; however, hemoglobin deficit appears related to fibroid presence rather than myomectomy itself. Neonatal outcomes were not adversely affected by cesarean myomectomy, whereas untreated fibroids appeared to be associated with lower birth weight. [J Turk Ger Gynecol Assoc. 2026; 27(3): 187-95]

Keywords: Cesarean myomectomy, uterine fibroids, maternal outcomes, neonatal outcomes

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Introduction

Uterine leiomyomas (fibroids) are the most common benign tumors of the female reproductive system and frequently coexist with pregnancy (1). Although the overall prevalence of fibroids in pregnancy varies widely depending on diagnostic modality and population characteristics, recent studies estimate rates ranging from approximately 2% to 12% in pregnant women, with higher prevalence reported in advanced maternal age and multiparous populations (2,3). Fibroids originate from monoclonal proliferation of smooth muscle cells within the myometrium and exhibit heterogeneous growth patterns influenced by hormonal, genetic, and vascular factors. Given their high prevalence, fibroids represent a frequent clinical challenge in obstetric practice.

While many fibroids remain asymptomatic during pregnancy, their presence has been associated with a spectrum of obstetric complications, including malpresentation, preterm birth, placental abruption, cesarean delivery, and postpartum hemorrhage (4,5). Fibroid size, number, and location, and in particularly large intramural or lower-segment myomas that may obstruct the uterine incision site or alter placental perfusion, appear to play an important role in determining obstetric risk. In addition to maternal morbidity, fibroid-related alterations in uterine architecture and perfusion may influence fetal growth and neonatal outcomes, although findings remain inconsistent across studies (6-8).

Management of uterine fibroids at the time of cesarean section (CS) represents one of the most debated topics in contemporary obstetric surgery. Historically, cesarean myomectomy was discouraged due to concerns regarding uncontrollable hemorrhage, prolonged operative time, and increased risk of peripartum hysterectomy (9,10). Consequently, fibroid removal during cesarean delivery was traditionally limited to pedunculated or easily accessible subserosal lesions. However, advances in surgical techniques, anesthesia, hemostatic strategies, and perioperative blood management have prompted renewed interest in the safety and feasibility of cesarean myomectomy.

In recent years, multiple observational studies and meta-analyses have reported comparable maternal outcomes between cesarean myomectomy and cesarean delivery without myomectomy in selected patient populations, particularly when procedures are performed by experienced surgeons. Reported outcomes suggest that although cesarean myomectomy may be associated with increased operative complexity, rates of transfusion, severe hemorrhage, and hysterectomy are not consistently higher than those observed in patients with fibroids who do not undergo myomectomy. Nevertheless, heterogeneity in study design, patient selection, fibroid characteristics, perioperative management and outcome definitions have limited the generalizability of existing evidence, and current international guidelines remain cautious, emphasizing individualized decision-making rather than universal recommendations (11).

Importantly, many prior studies have focused primarily on comparisons between cesarean myomectomy and cesarean delivery without fibroids, potentially confounding the effects of fibroid presence with those of surgical intervention (10,12). Fewer investigations have incorporated a three-group comparative framework that separately evaluates patients undergoing cesarean myomectomy, patients with fibroids managed conservatively at cesarean delivery, and patients without fibroids. Such a design is essential to disentangle the contribution of fibroid burden itself from the incremental impact of myomectomy on maternal hematologic parameters, transfusion requirements, and postoperative recovery. This limitation hampers accurate risk stratification and may lead to overly conservative or inconsistent surgical decision-making in contemporary obstetric practice.

Therefore, the aim of the present study was to comprehensively compare maternal and neonatal outcomes among three distinct groups and to disentangle the impact of fibroid burden itself from the incremental effects of myomectomy at the time of cesarean delivery. The primary outcomes included perioperative changes in hemoglobin and hematocrit levels, transfusion requirement, and length of hospital stay. Secondary outcomes focused on neonatal parameters, including birth weight, birth length , and Apgar scores. By employing a three-group analytical approach, it was hoped to provide clinically relevant evidence to inform surgical decision-making regarding cesarean myomectomy.

Material and Methods

This retrospective cohort study was conducted between May 2017 and December 2024. The study included pregnant women who delivered via CS. Approval from the University of Health Sciences Türkiye, Balıkesir Atatürk City Hospital Ethics Committee was sought prior to the study and it conforms to the provisions of the Declaration of Helsinki (approval no: 2025/02/20, date: 20.02.2025). As this was a retrospective study, informed consent was waived. Inclusion criteria consisted of women aged 18 years or older with no additional comorbidities. This approach was adopted to minimize confounding effects of systemic comorbidities on perioperative and neonatal outcomes. Exclusion criteria included patients with ovarian cysts, any malignancy, diabetes, hypertension, other chronic diseases, and multiple pregnancies.

Demographic and clinical data were retrospectively extracted from the hospital's electronic medical record system. Maternal variables included age, gestational age at delivery, body mass

index (BMI), gravidity, parity, and abortion history. BMI was calculated as weight (kg) divided by height squared (m^2). Laboratory parameters included preoperative and postoperative hemoglobin, hematocrit, platelet count, neutrophil count, and lymphocyte count. Additional variables included transfusion requirement, length of hospital stay, and myoma-related characteristics (number of myomas, total myoma volume, and maximum myoma volume). Neonatal outcomes included birth weight, birth length , and Apgar scores at 1 and 5 minutes.

Myoma volume was calculated using the ellipsoid formula ($V = \pi/6 \times length \times width \times depth$). Total myoma volume (total V) was defined as the sum of volumes of all detected myomas, and the largest individual myoma volume was defined as maximum myoma volume (max V). Laboratory analyses were performed using AU5800 (Beckman Coulter, California, USA) and pocH-100i (Sysmex Corporation, Japan). The same reagent kits and internal quality control procedures were used throughout the study period. None of the fibroids included in the study were submucosal. The majority of lesions were subserosal or intramural-subserosal fibroids.

Patients were categorized into three groups: Group 1, CS with concomitant myomectomy; Group 2, CS in the presence of uterine myomas without myomectomy; and Group 3, CS without uterine myomas. Group 3 was selected to match the sample size of the cesarean myomectomy group, allowing balanced three-group comparisons. A post-hoc power analysis was performed assuming an 80% power, a 95% confidence level, and a 5% margin of error. Myomectomy in Group 1 was performed during CS by experienced obstetric surgeons. Hemostasis during cesarean myomectomy was achieved using electrocautery, uterine compression sutures, and routine oxytocin infusion. No additional vasoconstrictive agents, such as vasopressin, were used, and uterine artery ligation or balloon tamponade was not routinely performed. Group 3 patients were consecutively selected from women without uterine myomas who underwent CS during the same study period.

Statistical analysis

All statistical analyses were performed using Stata version 17 (StataCorp, USA). Normality of continuous variables was assessed using the Shapiro-Wilk test. Normally distributed variables were analyzed using one-way analysis of variance (ANOVA), while non-normally distributed variables were analyzed using the Kruskal-Wallis test. Post-hoc pairwise comparisons were performed using Tukey's test for ANOVA and Dunn's test with Bonferroni correction for Kruskal-Wallis analyses. Two-group comparisons were conducted using the independent samples t-test or the Mann-Whitney U test, as appropriate. Categorical variables were analyzed using the chi-square test or Fisher's exact test.

Exploratory binary logistic regression analyses were performed to evaluate factors associated with transfusion requirement and group discrimination. Given the observational design, these models were intended for hypothesis generation rather than causal inference. The discriminative performance of these models was assessed using receiver operating characteristic (ROC) curve analysis and area under the curve (AUC) values. To evaluate sample adequacy, a post-hoc power analysis was conducted using one-way ANOVA with three groups. Assuming a medium effect size (Cohen's $f = 0.25$), an alpha level of 0.05, and the observed group sizes, the calculated statistical power was 0.9999. This analysis was performed to confirm sample adequacy rather than to guide study design. A p-value <0.05 was considered statistically significant.

Results

Baseline characteristics

The study cohort numbered 682 with 252 (36.95%), 178 (26.1%) and 252 (36.95%) women in Groups 1, 2 and 3, respectively. Baseline demographic and obstetric characteristics are presented in Table 1. Statistically significant differences were observed between the three groups with respect to maternal age, gestational age at delivery, number of previous abortions, systolic blood pressure, diastolic blood pressure, and neonatal birth weight (all $p<0.05$). BMI, gravidity, parity, and neonatal birth length were comparable across groups ($p>0.05$).

Preoperative hemoglobin level, hematocrit, platelet count, neutrophil count, and lymphocyte count did not differ significantly between the groups (Table 2). In contrast, postoperative hemoglobin level, hematocrit, and platelet count differed significantly among the three groups (Table 2).

Pairwise comparisons demonstrated no statistically significant difference in hemoglobin deficit between Group 1 and Group 2 ($p=0.346$). However, hemoglobin deficit was significantly greater in both Group 1 and Group 2 compared with Group 3 ($p<0.05$ for both comparisons) (Figure 1). Hematocrit deficit was significantly greater in Group 1 than in Group 2 and Group 3 ($p<0.05$ for both comparisons). Similarly, change in platelet count was significantly greater in Group 1 compared with both Group 2 and Group 3 ($p<0.05$) (Figure 2).

The rate of blood transfusion requirement differed significantly between the three groups ($p<0.05$), with the highest transfusion rate observed in Group 1. Length of hospital stay also differed significantly between groups ($p<0.05$). When analyzed according to transfusion status, patients who received transfusions had significantly longer hospital stays compared with those who did not in all three groups (all $p<0.05$). Group-specific hospitalization data stratified by transfusion status are presented in Table 3.

Neonatal outcomes are summarized in Table 4. A significant difference was observed in birth weight between the three

Table 1. Demographic comparison of three groups

Variable	Group 1 (mean ± SD)	Group 2 (mean ± SD)	Group 3 (mean ± SD)	p-value
Age (years)	31.16±4.37	32.42±5.78	31.18±6.08	p<0.05
Gestational age (weeks)	37.79±1.72	37.72±1.20	37.78±1.12	p<0.05
BMI (kg/m^2)	30.32±2.96	30.98±3.51	30.75±3.36	0.3076
Gravidity	1.73±0.90	1.58±0.77	1.56±0.77	0.0833
Parity	0.57±0.69	0.52±0.74	0.48±0.73	0.1343
Abortion	0.16±0.47	0.06±0.23	0.07±0.25	p<0.05
SBP (mmHg)	115.73±8.22	110.98±15.01	111.83±14.89	p<0.05
DBP (mmHg)	70.30±6.33	67.50±9.48	68.15±8.77	p<0.05
Birth weight (gr)	3130.15±642.09	3000.96±441.61	3157.90±481.60	p<0.05
Birth length (cm)	49.47±2.72	49.76±1.44	49.79±1.34	0.9852

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, SD: Standard deviation, BMI: Body mass index. p-values were obtained using the Kruskal-Wallis test

Table 2. Preoperative and postoperative laboratory values among study groups

Variable	Group 1 (mean ± SD)	Group 2 (mean ± SD)	Group 3 (mean ± SD)	p-value
Pre-HGB	12.11±0.07	12.03±0.08	11.96±0.09	0.443
Pre-HCT	36.11±0.21	36.08±0.24	35.9±0.27	0.804
Pre-PLT	249.81±3.921	259.06±4.822	258.31±5.331	0.212
Pre-NEU	7.02±0.11	7.18±0.12	7.31±0.14	0.191
Pre-LYM	1.99±0.03	1.99±0.03	1.96±0.04	0.850
Post-HGB	10.83±0.08	11.46±0.07	10.77±0.08	p<0.05
Post-HCT	32.82±0.21	34.09±0.21	34.02±0.24	p<0.05
Post-PLT	206.5±3.91	233.22±4.48	232.4±4.91	p<0.05
Post-NEU	11.13±0.19	11.31±0.17	11.43±0.21	0.287
Post-LYM	3.05±1.36	3.07±1.35	3.64±1.92	0.835

HGB: Hemoglobin, HCT: Hematocrit, PLT: Platelet, NEU: Neutrophil, LYM: Lymphocyte, SD: Standard deviation

groups (p<0.05). Pairwise comparisons revealed that birth weight was significantly lower in Group 2 compared with Group 1 (p<0.05) and Group 3 (p<0.05), whereas no significant difference was observed between Group 1 and Group 3 (p=0.956) (Table 5). No statistically significant differences were found between the groups with respect to neonatal birth length or Apgar scores at 1 and 5 minutes (all p>0.05).

Among patients with uterine fibroids (Groups 1 and 2), myoma-related characteristics differed significantly between groups. Maximum myoma volume was significantly higher in Group 1, whereas myoma count was significantly higher in Group 2 (both p<0.05). Total myoma volume did not differ significantly between the two groups (p=0.09).

Subgroup analyses based on myoma number demonstrated that patients with multiple fibroids had significantly higher total myoma volume and maximum myoma volume compared with patients with a single fibroid (both p<0.05). In contrast, change in hemoglobin level, transfusion requirement rate, and length of hospital stay did not differ significantly between patients with single or multiple fibroids (all p>0.05). Neonatal outcomes, including birth weight and Apgar scores, were also comparable between the two subgroups (Supplementary Table 1).

The relationship between myoma count and perioperative outcomes is illustrated in Figure 3. Higher median hemoglobin change and longer hospital stay were observed across increasing myoma count categories. Transfusion rates also varied according to myoma count categories. Descriptive trends across myoma count groups are presented without formal statistical comparison.

When transfusion status was evaluated according to myoma burden, patients who received transfusions had higher total myoma volume and maximum myoma volume compared with those who did not. However, these differences did not reach

statistical significance in pairwise analyses (Group 1: p=0.082; Group 2: p=0.210) (Table 6).

ROC analyses comparing patient groups demonstrated variable discriminative performance. The comparison between patients who underwent cesarean myomectomy and patients with fibroids who did not undergo myomectomy (Group 1 vs. Group 2) showed excellent discrimination (AUC =0.92). Comparisons between Group 1 and fibroid-free controls (Group 3) and between Group 2 and Group 3 demonstrated good discriminative performance, with AUC values of 0.81 and 0.82, respectively (Figure 4).

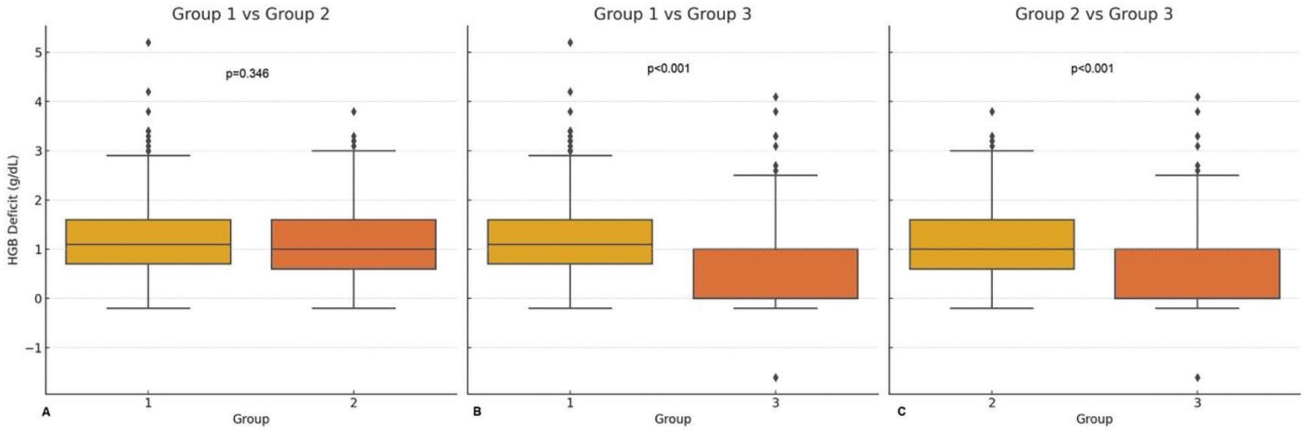

Figure 1. The boxplot comparison of pre-post hemoglobin (HGB) deficit among the three study groups. (A) There was no statistically significant difference in HGB deficit between Group 1 and Group 2. (B) A statistically significant difference was observed between Group 1 and Group 3. (C) A statistically significant difference was observed between Group 2 and Group 3. Mann-Whitney U test

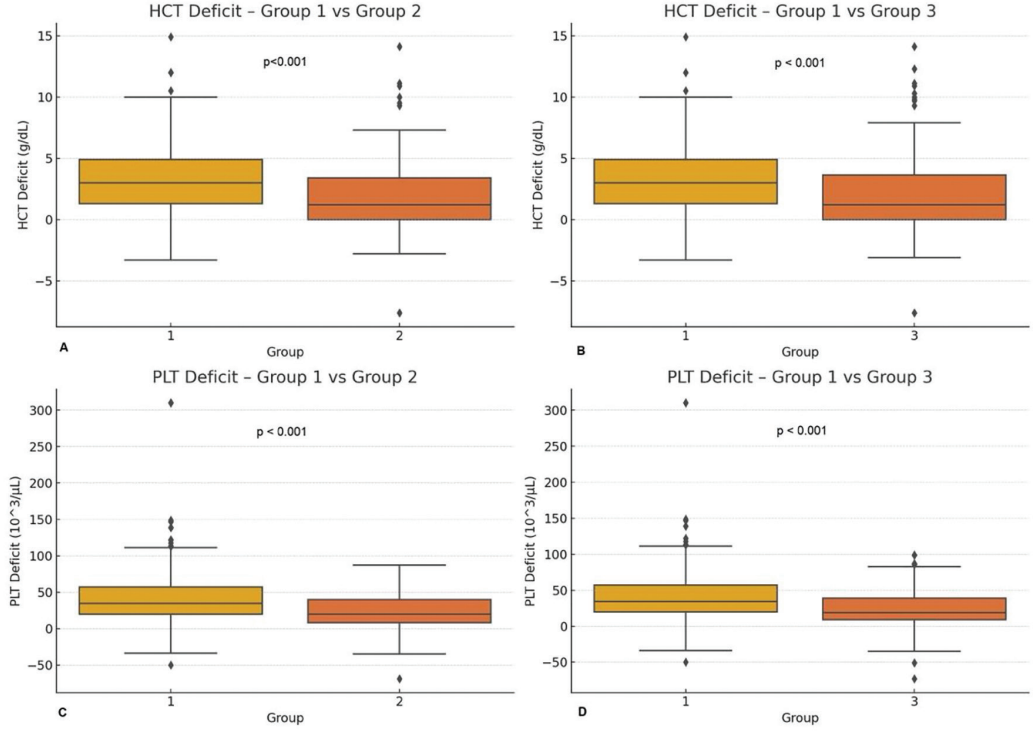

Figure 2. The boxplot comparison of pre-post hemoglobin, hematocrit (HCT) and platelet (PLT) deficit in pairwise group comparisons. (A) Group 1 had significantly greater HCT deficit than Group 2. (B) HCT deficit was significantly higher in Group 1 compared to Group 3. (C) PLT counts showed a significantly greater deficit in Group 1 compared to Group 2. (D) Group 1 demonstrated significantly higher PLT deficit compared to Group 3

In a separate exploratory logistic regression model evaluating factors associated with the decision to perform myomectomy, limited discriminative ability was observed (AUC =0.602). The corresponding ROC curve is presented in Figure 5.

Discussion

The present study set out to provide a comprehensive comparison of maternal and neonatal outcomes among women undergoing CS with concomitant myomectomy, women with uterine fibroids managed conservatively at cesarean delivery, and women without fibroids. By employing a three-group design of 682 patients, our findings allow differentiation between the effects attributable to fibroid burden itself and those related specifically to the myomectomy procedure. Uterine fibroids may undergo variable changes in size during pregnancy. Recent evidence indicates that most fibroids either remain stable or increase only modestly in volume, particularly during the first trimester. Rapid fibroid enlargement is relatively uncommon and is often followed by stabilization or even regression later in pregnancy, likely due to changes in uterine blood flow and fibroid degeneration (4,13).

Table 3. Hospitalization duration by transfusion status

Group	Transfusion	Mean ± SD	Count
Group 1	No	1.94±0.43	241
Group 1	Yes	2.82±0.40	11
Group 2	No	1.86±0.49	170
Group 2	Yes	2.62±0.74	8
Group 3	No	1.92±0.46	241
Group 3	Yes	2.73±0.65	11
p<0.05 for comparisons between transfusion and non-transfusion subgroups within each study group (Mann-Whitney U test). SD: Standard deviation			

Table 4. Neonatal outcomes-group comparisons

Parameter	Test	p-value
Birth weight	Kruskal-Wallis	p<0.05
Birth length	Kruskal-Wallis	0.9852
Apgar 1	Kruskal-Wallis	0.9958
Apgar 5	Kruskal-Wallis	0.9958
Kruskal-Wallis test (3-group comparison)		

Table 5. Pairwise Mann-Whitney U tests (birth weight)

Comparison	Test	p-value
Group 1 vs. Group 2	Mann-Whitney U	p<0.05
Group 1 vs. Group 3	Mann-Whitney U	0.9558
Group 2 vs. Group 3	Mann-Whitney U	p<0.05

Table 6. Association between myoma burden and transfusion requirement

Group	Mean total V (transfusion)	Mean total V (no transfusion)	p-value
Group 1	68.911	17.004	0.082
Group 2	15.969	13.584	0.21
total V: Total myoma volume			

Consistent with prior observational studies (10,14), cesarean myomectomy in our cohort was associated with a greater magnitude of perioperative hematologic changes and higher transfusion rates compared with cesarean delivery in women without fibroids. However, a key finding of this study was that hemoglobin deficit did not differ significantly between patients undergoing cesarean myomectomy and those with fibroids who did not undergo myomectomy (p=0.346). This observation suggests that the presence of uterine fibroids, rather than the act of myomectomy itself, represents the dominant contributor to perioperative blood loss. This finding may partially be explained by impaired uterine contractility associated with fibroid-containing uteri. Fibroids can disrupt normal myometrial architecture and interfere with effective uterine contraction after delivery, thereby contributing to increased perioperative blood loss independent of myomectomy itself. In contrast, changes in hematocrit and platelet values were more pronounced in the cesarean myomectomy group. These findings likely reflect increased surgical manipulation and local hemostatic consumption associated with fibroid enucleation. Importantly, however, these laboratory differences did not translate into disproportionately higher rates of severe maternal morbidity, supporting the notion that cesarean myomectomy imposes an increased but clinically manageable hematologic burden when performed in appropriately selected patients.

The higher transfusion rate observed in the cesarean myomectomy group aligns with previous reports (6,14), yet our subgroup analyses further clarify this relationship. Transfusion requirement was more closely related to postoperative hemoglobin levels and platelet counts than to fibroid number or total fibroid volume alone. On the other hand, some studies reported no significant difference in blood transfusion rates between women who underwent cesarean myomectomy and those who had cesarean delivery without myomectomy (15,16). These findings suggest that, in appropriately selected patients and in experienced centers, cesarean myomectomy does not confer an additional transfusion risk compared with CS alone. In our study, hospitalization duration was significantly prolonged in transfused patients across all groups, underscoring transfusion status as a marker of postoperative recovery rather than a procedure-specific complication.

Collectively, these findings further support the notion that perioperative blood loss is strongly influenced by the presence of uterine fibroids rather than the myomectomy procedure itself. Although cesarean myomectomy was associated with greater hematocrit and platelet changes, these likely reflect increased surgical manipulation and localized hemostatic consumption rather than uncontrolled hemorrhage. Importantly, no major myomectomy-related perioperative or postoperative complications, including puerperal sepsis or secondary postpartum hemorrhage, were observed in our cohort.

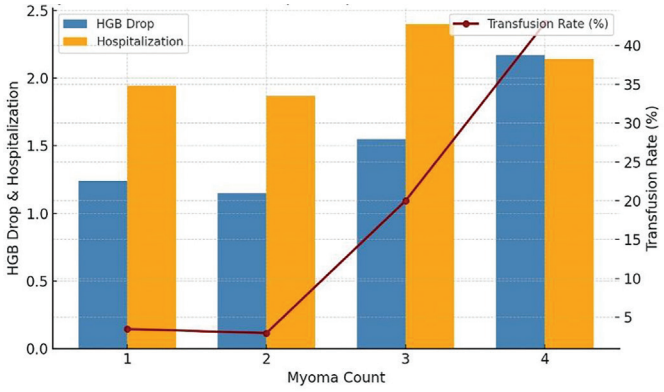

Figure 3. Distribution of perioperative outcomes according to myoma count. The figure demonstrates hemoglobin deficit, length of hospital stay, and transfusion rate across different myoma count categories. Values are presented descriptively to illustrate trends in perioperative outcomes according to myoma burden

HGB: Hemoglobin

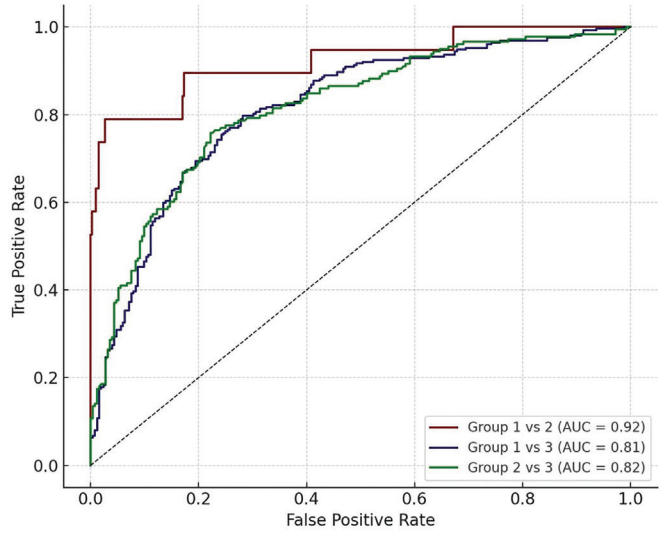

Figure 4. Logistic regression and receiver operating characteristic analyses for group discrimination

AUC: Area under the curve

An important contribution of this study is the detailed evaluation of fibroid characteristics and their relationship to surgical decision-making. Patients undergoing cesarean myomectomy tended to have larger maximum fibroid volumes, whereas patients with fibroids managed conservatively more frequently exhibited a higher number of smaller fibroids. However, total fibroid volume did not differ significantly between these groups, suggesting that surgeons may prioritize accessibility and dominant lesion size over cumulative fibroid burden when deciding whether to perform myomectomy at the time of cesarean delivery. This approach is consistent with previous reports indicating that fibroid size and localization, rather than total fibroid load, play a central role in determining the feasibility and safety of cesarean myomectomy. Several studies have emphasized that larger, subserosal or pedunculated fibroids are more frequently selected for removal during cesarean delivery, whereas multiple smaller or intramural fibroids are often managed conservatively due to concerns regarding bleeding and operative complexity (16-18). Collectively, these findings support the concept that dominant fibroid characteristics, particularly size and surgical accessibility, are key determinants of intraoperative decision-making in cesarean myomectomy.

Subgroup analyses comparing single versus multiple fibroids further support this interpretation. Although patients with multiple fibroids had significantly higher total and maximum fibroid volumes, hemoglobin deficit, transfusion rate, and length of hospital stay were comparable between single and multiple

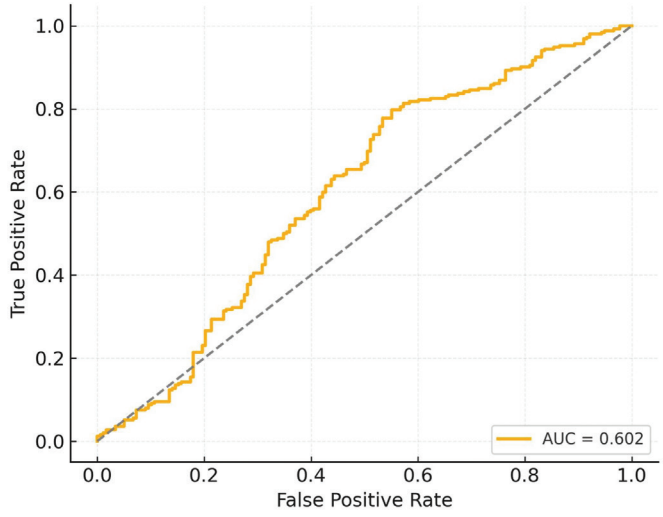

Figure 5. Receiver operating characteristic curve for the logistic regression model predicting myomectomy decision during cesarean section. The model includes predictors such as max V, myoma count, total V, BMI, age, and gestational age. AUC =0.602, indicating moderate predictive performance

AUC: Area under the curve, max V: Maximum myoma volume, total V: Total myoma volume, BMI: Body mass index

fibroid subgroups. These findings imply that fibroid number alone may be a poor predictor of perioperative risk and that surgical feasibility is likely influenced by fibroid location, accessibility, and surgeon experience rather than numeric burden.

The exploratory logistic regression model evaluating factors associated with the decision to perform myomectomy demonstrated limited discriminative ability, reinforcing the complexity and individualized nature of intraoperative decision-making. Taken together, these results emphasize that cesarean myomectomy is not governed by a single quantitative threshold but rather by a constellation of anatomical and clinical considerations. In our institution, the decision to perform cesarean myomectomy was individualized and based primarily on intraoperative surgical assessment, including fibroid accessibility, dominant lesion size, technical feasibility, and perceived hemorrhage risk rather than predefined standardized criteria.

One of the most clinically relevant findings of this study relates to neonatal outcomes. Neonates born to mothers with fibroids who did not undergo myomectomy exhibited significantly lower birth weight compared with both cesarean myomectomy patients and fibroid-free controls. In contrast, birth weight did not differ between the cesarean myomectomy group and women without fibroids. Apgar scores and neonatal length were comparable across all groups. The significantly lower birth weight observed in patients with untreated fibroids suggests that the persistence of fibroids during pregnancy may negatively influence fetal growth. In contrast, birth weight in the cesarean myomectomy group was comparable to that of fibroid-free controls. Potential mechanisms include mechanical distortion of the uterine cavity and compromised uteroplacental perfusion. Fibroid localization may also influence neonatal outcomes. In particular, fibroids located near the lower uterine segment or uterine incision site may interfere with placental implantation, uterine distensibility, and local perfusion, potentially exerting a greater impact on fetal growth. These findings likely reflect the biological and mechanical effects of fibroids during pregnancy rather than the effect of cesarean delivery itself. However, fibroids directly involving the uterine incision site were not present in our cohort. Moreover, detailed localization data were not uniformly available in this retrospective study, limiting further subgroup analyses according to fibroid location. Notably, neonatal outcomes in the cesarean myomectomy group were comparable to those of fibroid-free patients, supporting the neonatal safety of myomectomy when performed under controlled conditions. These findings are consistent with previous studies reporting an association between untreated uterine fibroids and reduced neonatal birth weight, particularly in cases involving larger or strategically located fibroids (19,20). Prior literature has suggested that fibroids may impair placental development and uteroplacental blood flow, thereby contributing to fetal growth restriction. Importantly, available evidence indicates that removal of selected fibroids at the time of cesarean delivery does not negatively affect neonatal outcomes, reinforcing the concept that cesarean myomectomy can mitigate fibroid-related growth impairment without compromising neonatal safety.

Recent systematic reviews and meta-analyses have increasingly challenged the traditional avoidance of cesarean myomectomy, reporting comparable rates of major maternal complications between cesarean myomectomy and cesarean delivery alone in selected populations. Our findings are concordant with this evolving body of evidence while adding nuance through the inclusion of a fibroid-positive non-myomectomy comparison group. This three-arm design highlights that fibroid presence itself constitutes a meaningful risk factor for both maternal hematological changes and neonatal growth restriction, independent of surgical intervention.

Study limitations

The strengths of this study include its large sample size, three-group comparative design, detailed assessment of hematological parameters, and comprehensive evaluation of fibroid characteristics. The inclusion of both maternal and neonatal outcomes provides a balanced assessment of perioperative safety and fetal well-being. Several limitations should be acknowledged. The retrospective nature of the study limits causal inference and introduces potential selection bias, particularly regarding the decision to perform myomectomy. Although major fibroid localization patterns were available, detailed standardized classification data for all fibroids, as well as surgeon-specific operative parameters including operative time and estimated blood loss, were not uniformly available. In addition, long-term maternal outcomes, such as fibroid recurrence and future fertility, could not be assessed. Finally, although neonatal outcomes were reassuring, long-term neonatal follow-up was beyond the scope of this analysis.

Despite these limitations, our findings contribute meaningful evidence to the ongoing debate surrounding cesarean myomectomy. Importantly, the heterogeneity of existing studies-particularly with respect to fibroid characteristics, surgeon experience, and institutional resources-has limited the development of universal guidelines. The results suggest that, in selected patients, cesarean myomectomy can be performed without compromising neonatal outcomes and without imposing disproportionate maternal risk beyond that associated with fibroid presence itself. These data support a shift from a uniformly conservative approach toward a more individualized, anatomy-driven surgical strategy. Our results support a more individualized approach, emphasizing patient selection, surgical

expertise, and intraoperative assessment rather than categorical avoidance or endorsement of cesarean myomectomy.

Conclusion

Cesarean myomectomy appears to be a feasible and clinically acceptable option in selected patients when performed by experienced surgeons. The presence of uterine fibroids themselves may contribute more substantially to perioperative hematological changes and adverse neonatal growth outcomes than the myomectomy procedure itself. Future prospective studies with standardized reporting of fibroid characteristics, surgical techniques, and perioperative management are warranted to further refine patient selection criteria. Randomized trials may be challenging in this context but well-designed multicenter registries could provide high-quality evidence to guide clinical decision-making and inform guideline development.

Ethics

Ethics Committee Approval: *Approval from the University of Health Sciences Türkiye, Balıkesir Atatürk City Hospital Ethics Committee was sought prior to the study and it conforms to the provisions of the Declaration of Helsinki (approval no: 2025/02/20, date: 20.02.2025).*

Informed Consent: *As this was a retrospective study, informed consent was waived.*

Footnotes

Author Contributions: *Surgical and Medical Practices: Ç.B.B., V.K., S.T.Y., Concept: Ç.B.B., Design: Ç.B.B., Data Collection or Processing: Ç.B.B., S.T.Y., Analysis or Interpretation: Ç.B.B., V.K., Literature Search: Ç.B.B., V.K., Writing: Ç.B.B.*

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References

1. Li B, Wang F, Chen L, Tong H. Global epidemiological characteristics of uterine fibroids. Arch Med Sci. 2023; 19: 1802-10.
2. Wang HM, Tian YC, Xue ZF, Zhang Y, Dai YM. Associations between uterine fibroids and obstetric outcomes in twin pregnancies. Int J Gynaecol Obstet. 2016; 135: 22-7.
3. Mitro SD, Peddada S, Chen Z, Buck Louis GM, Gleason JL, Zhang C, et al. Natural history of fibroids in pregnancy: National Institute of Child Health and Human Development Fetal Growth Studies - Singletons cohort. Fertil Steril. 2022; 118: 656-65.
4. Coutinho LM, Assis WA, Spagnuolo-Souza A, Reis FM. Uterine fibroids and pregnancy: how do they affect each other? Reprod Sci. 2022; 29: 2145-51.
5. Tîrnovanu MC, Lozneanu L, Tîrnovanu ŞD, Tîrnovanu VG, Onofriescu M, Ungureanu C, et al. Uterine fibroids and pregnancy: a review of the challenges from a romanian tertiary level institution. Healthcare (Basel). 2022; 10: 855.
6. Ramasauskaite D, Purandare N, Diaz I, Kvederaite-Budre G, Beyuo TK, Beyeza-Kashesya J, et al. Fibroids and pregnancy. Int J Gynaecol Obstet. 2026; 172: 51-8.
7. Li H, Hu Z, Fan Y, Hao Y. The influence of uterine fibroids on adverse outcomes in pregnant women: a meta-analysis. BMC Pregnancy Childbirth. 2024; 24: 345.
8. Al Sulaimani R, Machado L, Al Salmi M. Do large uterine fibroids impact pregnancy outcomes? Oman Med J. 2021; 36: e292.
9. Goyal M, Dawood AS, Elbohoty SB, Abbas AM, Singh P, Melana N, et al. Cesarean myomectomy in the last ten years; a true shift from contraindication to indication: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2021; 256: 145-57.
10. Youshanloie MM, Vaezi M, Pashazadeh F. Consequences of concurrent myomectomy and caesarean section versus caesarean section alone in the last two decades: systematic review and meta-analysis. Current Women's Health Reviews. 2023; 19: 14.
11. ACOG Practice Bulletin No. 228: Management of symptomatic uterine leiomyomas: correction. Obstet Gynecol. 2021; 138: 683.
12. Tinelli A, Nezhat CH, Likić-Ladjević I, Andjić M, Tomašević D, Papoutsis D, et al. Myomectomy during cesarean section or non-caesarean myomectomy in reproductive surgery: this is the dilemma. Clin Exp Obstet Gynecol. 2021; 48: 1250-8.
13. Vitagliano A, Noventa M, Di Spiezio Sardo A, Saccone G, Gizzo S, Borgato S, et al. Uterine fibroid size modifications during pregnancy and puerperium: evidence from the first systematic review of literature. Arch Gynecol Obstet. 2018; 297: 823-35.
14. Lee YE, Park S, Lee KY, Song JE. Risk factors based on myoma characteristics for predicting postoperative complications following cesarean myomectomy. PLoS One. 2023; 18: e0280953.
15. Pergialiotis V, Sinanidis I, Louloudis IE, Vichos T, Perrea DN, Doumouchtsis SK. Perioperative complications of cesarean delivery myomectomy: a meta-analysis. Obstet Gynecol. 2017; 130: 1295-303.
16. El-Refaie W, Hassan M, Abdelhafez MS. Myomectomy during cesarean section: a retrospective cohort study. J Gynecol Obstet Hum Reprod. 2020: 101900.
17. Akbas M, Mihmanli V, Bulut B, Temel Yuksel I, Karahisar G, Demirayak G. Myomectomy for intramural fibroids during caesarean section: a therapeutic dilemma. J Obstet Gynaecol. 2017; 37: 141-5.
18. Zhao R, Wang X, Zou L, Zhang W. Outcomes of myomectomy at the time of cesarean section among pregnant women with uterine fibroids: a retrospective cohort study. Biomed Res Int. 2019; 2019: 7576934.
19. Huang Y, Ming X, Li Z. Feasibility and safety of performing cesarean myomectomy: a systematic review and meta-analysis. J Matern Fetal Neonatal Med. 2022; 35: 2619-27.
20. Barati M, Saadati N, Jalili Z, Moramezi H. Demographic, clinical characteristics and maternal-neonatal outcomes in patients undergoing cesarean myomectomy. Shiraz E-Med J. 2025; 26: e163314.

Double stimulation in the same menstrual cycle (DuoStim): a comparative evaluation of follicular and luteal phase response

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Abstract

Objective: Double ovarian stimulation (DuoStim) protocols, in which both follicular and luteal phase stimulations are performed within the same menstrual cycle, have emerged as a promising strategy for patients with diminished ovarian reserve. The aim of this study is to compare the outcomes of follicular and luteal phase stimulations in patients undergoing DuoStim protocols.

Material and Methods: This retrospective intra-patient paired comparative study included patients who underwent DuoStim between January 2018 and December 2024 at a university-based infertility clinic. Stimulation protocols, gonadotropin doses and trigger types were evaluated. Primary outcomes were retrieved oocyte and metaphase II (MII) oocyte numbers across both stimulation phases. Clinical pregnancy rates achieved by embryos derived separately from each stimulation phase were evaluated as a secondary outcome. Duration of stimulation, total gonadotropin doses administered, cumulative oocyte yield and embryos obtained, fertilization rates, implantation rates, and live birth rates were also assessed.

Results: The study included 120 patients. Retrieved oocytes numbers [2 (1-3) and 2 (1-5) in follicular phase and luteal phase], MII oocytes [1 (1-2) and 2 (0-4)], and frozen cleavage stage embryos [1 (0-1) and 1 (0-2) in follicular phase and luteal phase] were higher in the luteal phase stimulation ($p<0.001$, $p=0.001$, and $p=0.005$ respectively). Oocyte yield, fertilization rates, implantation rates, and clinical pregnancy rates were similar between the two phases. Total gonadotropin doses and stimulation duration were significantly higher during follicular phase stimulation.

Conclusion: In patients with diminished ovarian reserve undergoing DuoStim, luteal phase stimulation yielded significantly more retrieved oocytes and MII oocytes despite requiring lower gonadotropin doses and shorter stimulation duration. Fertilization rates, embryo development, and clinical pregnancy rates were comparable between phases, suggesting that luteal phase-derived embryos are equally competent. These findings support DuoStim as an effective strategy to maximize oocyte yield within a single menstrual cycle in this challenging population. Further prospective studies are warranted to evaluate cumulative reproductive outcomes. [J Turk Ger Gynecol Assoc. 2026; 27(3): 196-202]

Keywords: Diminished ovarian reserve, double stimulation, DuoStim, ovarian stimulation

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Introduction

Follicular growth is believed to occur in multiple waves enabling recruitable antral follicles in the ovaries throughout the entire menstrual cycle (1). Based on this physiological understanding, in assisted reproductive technology, particularly in patients with diminished ovarian reserve, two consecutive stimulations may be performed within the same cycle to increase the number of oocytes retrieved in a shorter time and enhance the likelihood of obtaining more embryos (2). However, studies investigating

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this protocol, referred to as "double stimulation" or "DuoStim," remain limited.

It has been reported that better reproductive outcomes can be achieved with the continuation of the second stimulation after the conventional protocol in cases of diminished ovarian reserve (3). Nonetheless, results of studies comparing follicular and luteal phase efficiency are conflicting. Some studies indicate that oocytes retrieved during follicular phase stimulation exhibit higher quality and fertilization rates compared to those from luteal phase stimulation (4,5), while others report a superior ovarian response in luteal phase stimulation or find no significant difference between the two phases (6-8). Moreover, the interval between oocyte retrieval and the initiation of luteal phase stimulation varies across studies, and the optimal timing to achieve the most effective ovarian response is unclear (5).

The aim of this study was to compare the reproductive outcomes of follicular and luteal phase stimulation in patients undergoing double stimulation within the same cycle. A particular question of interest was the comparison of clinical pregnancy rates obtained with embryos derived from both stimulation phases separately.

Material and Methods

This study was conducted as a retrospective intra-patient paired comparative study. Data of patients who underwent two consecutive stimulations double ovarian stimulation (DuoStim) in the same cycle between January 2018 and December 2024 in the Reproductive Endocrinology and Infertility Department of a Başkent University Faculty of Medicine were evaluated. Follicular phase- and luteal phase-derived oocytes and embryos, along with pregnancy outcomes obtained from these embryos, were compared. All patients who completed both stages of sequential stimulation in the same cycle due to diminished ovarian reserve/poor ovarian response during this period were included in the study. Diminished ovarian reserve is defined as anti-Müllerian hormone (AMH) <1.1 ng/mL or antral follicle count <7 (9). Patients with known endometrial anomalies, genetic anomalies, and recurrent implantation failure were excluded. Pre-implantation genetic testing cycles were not included.

Stimulation protocols

In our clinic, antagonist or progestin-primed ovarian stimulation (PPOS) protocols are routinely employed for controlled ovarian stimulation. Ovulation induction regimens were tailored to each patient's age, body mass index (BMI), and antral follicle count during both stimulation phases at the clinician's discretion. In the antagonist protocol, cetrorelix acetate (Cetrotide®, Merck, France) was initiated on the sixth day following the administration of 150-300 IU/day of gonadotropins, including follicle-stimulating hormone [(FSH); Gonal-f®, Merck, Italy] and/or human menopausal gonadotropin (Meriofert®, IBSA, Switzerland) (10). In the PPOS protocol, dydrogesterone (Duphaston® 10 mg, Abbott, Türkiye) was administered at a dose of 20 mg/day (2×10 mg) alongside gonadotropins (11). When at least one to two follicles reached ≥18 mm in diameter, final oocyte maturation was triggered using human chorionic gonadotropin [(hCG); Ovitrelle® 250 mcg, Merck, Türkiye] and/or a GnRH agonist (Decapeptyl® 0.1 mg, Ferring, Germany), and oocyte retrieval was performed 36 hours after the trigger (10).

Patients with diminished ovarian reserve were evaluated by ultrasonography at the oocyte retrieval day and if two or more follicles ≤10 mm were observed in one or both ovaries, luteal phase stimulation was initiated on the same day or within 6 days after oocyte retrieval. The preferred stimulation protocols and trigger agents were decided by clinical judgement. When at least one follicle reached ≥18 mm during the luteal phase, final triggering and oocyte retrieval were scheduled 36 hours later.

Retrieved oocytes were assessed for maturity, and intracytoplasmic sperm injection was performed on metaphase II (MII) oocytes. Fertilization was confirmed by the presence of two-pronuclear (2PN) zygotes 16-18 hours post-injection. Cleavage stage embryos were frozen on day 3, and blastocysts were cryopreserved on day 5/6. Only good-quality cleavage stage embryos and blastocysts were frozen. Good quality embryos were defined as cleavage stage embryos with ≥7 blastomeres, ≤10% fragmentation, uniform blastomeres, no or minimal vacuoles, and normal zona pellucida (Grade A or B); blastocysts were considered good quality at 3BB and above according to Gardner's classification (12).

Frozen embryo transfer protocol

All embryo transfers were frozen-thawed transfers performed with artificially prepared endometrium using hormone replacement therapy. Estradiol (E_2) hemihydrate (Estrofem® 2 mg, Novo Nordisk A/S, Denmark) 6 mg/day was initiated at day 3 of menstrual cycle and continued for at least 12 days. Endometrial thickness was measured by interval ultrasonography, and vaginal progesterone (P) (Progestan® 200 mg, Koçak Farma, Türkiye) 800 mg/day and subcutaneous P (Prolutex® 25 mg, IBSA, Türkiye) 25 mg/day were administered provided that endometrial thickness was ≥7 mm (11,13). Embryo transfer was performed on the fourth day of P supplementation for cleavage-stage embryos and on the sixth day for blastocyst-stage embryos (13). The presence of pregnancy was evaluated by measuring serum b-hCG value 12 days after embryo transfer. Clinical pregnancy was defined as presence of fetal cardiac activity on ultrasound investigation.

Outcome measures

Patient characteristics, including age, BMI and AMH levels were recorded. Cycle-related parameters, such as the stimulation protocols used in the follicular and luteal phases, duration of stimulation, total gonadotropin doses, trigger agents, and hormone levels on the trigger day were evaluated.

Primary outcomes were the cumulative number of oocytes retrieved and MII oocytes across both stimulation phases, reflecting the principal aim of DuoStim in this population. As a secondary outcome, clinical pregnancy rates achieved by embryos derived separately from each stimulation phase were compared. Additional secondary outcomes included fertilization rates, implantation rates, duration of stimulation, and total gonadotropin doses administered. The effect of the interval between oocyte retrieval and the initiation of luteal phase stimulation was also assessed.

Oocyte yield was defined as the ratio of the number of oocytes retrieved to the number of follicles ≥10 mm on the day of oocyte retrieval. Fertilization rate was defined as the ratio of 2PN zygotes to the number of MII oocytes used for fertilization. Implantation rate was calculated as the number of gestational sacs per embryo transferred. Pregnancy rate was defined as the number of clinical pregnancies per oocyte retrieval cycle from which an embryo transfer was performed (10).

This study was performed in line with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the Başkent University where the study was conducted (approval no: KA25/193; date: 19/06/2025). Informed consent for the use of medical data was obtained from all patients prior to their treatment.

Statistical analysis

SPSS, version 27.0 was used in the analysis of the data (IBM Inc., Armonk, NY, USA). Categorical measurements are presented as numbers and percentages, and continuous measurements are summarized with mean and standard deviation. For within-patient paired comparisons of continuous variables, paired sample t-tests were used when data were normally distributed, and Wilcoxon signed-rank tests were applied otherwise. For comparison of within-patient categorical variables McNemar's test was used. The effect of timing of luteal phase stimulation initiation on luteal phase outcomes were evaluated by Mann-Whitney U test (continuous variables) and chi-square test (categorical variables). In all tests, $p<0.05$ was considered statistically significant.

Results

A total of 120 patients who completed both phases of the double stimulation protocol during the specified study period were included. The mean age was 35.82±5.09 years, mean BMI was 24.04±4.04 kg/m^2, mean AMH level was 0.68±0.43 ng/mL, and mean antral follicle count was 5.21±2.63 (Table 1). The duration of stimulation and the total gonadotropin doses administered were significantly greater during follicular phase stimulation ($p<0.001$). The antagonist protocol was more frequently used during follicular phase stimulation (55.1%), whereas the PPOS protocol was predominantly used in luteal phase stimulation (81.3%) ($p<0.001$). On the trigger day, E_2 and P levels were significantly higher in luteal phase stimulation. Although dual trigger was widely used in both stimulation phases, it was significantly more frequent in the luteal phase (73.9%) ($p<0.001$) (Table 2). In follicular phase stimulation, there were no significant differences in retrieved oocyte rates, fertilization rates, frozen embryo rates, or implantation rates across different trigger types ($p>0.05$). However, in luteal phase stimulation, the fertilization rate was significantly higher in the dual trigger group ($p<0.001$).

Compared to follicular phase stimulation, luteal phase stimulation yielded a significantly higher number of retrieved oocytes [2 (1-3) vs. 2 (1-5) in follicular and luteal phases, respectively; $p<0.001$] and MII oocytes [1 (1-2) vs. 2 (0-4) in follicular and luteal phases, respectively; $p=0.001$]. Frozen cleavage embryo rates were also higher in luteal phase simulation [1 (0-1) vs. 1 (0-2); $p=0.005$] while frozen blastocyst numbers were similar between the two phases (Table 2).

Embryos were thawed for transfer in 68 of the 120 patients (56.7%): 43 patients had follicular phase embryos thawed and 43 had luteal phase embryos thawed, with 18 patients having embryos from both phases thawed. Embryo transfer was performed in 66 patients; transfer of follicular phase embryos in 5 patients, and luteal phase embryos in 4 patients, were deferred due to poor embryo quality following the thawing process.

Table 1. Baseline clinical characteristics of included patients

Clinical characteristics	Mean ± SD
Age (years)	35.82±5.09
BMI (kg/m^2)	24.04±4.04
AMH (ng/mL)	0.68±0.43
AFC	5.21±2.63

Values are presented as mean ± SD. AMH: Anti-Müllerian hormone, AFC: Antral follicle count, BMI: Body mass index, SD: Standard deviation

Table 2. Comparison of cycle parameters and outcomes between follicular and luteal phase stimulations (n=120 for each phase unless otherwise noted)

	Follicular phase stimulation (n=120) Median (IQR)	Luteal phase stimulation (n=120) Median (IQR)	p
Stimulation duration (days)	7 (6-9)	6 (4-8)	**0.004**
Total gonadotropin dose (IU)	2100 (1500-2700)	1500 (1068.7-2306.2)	**0.002**
Stimulation protocol, n (%)			**<0.001**
None	4.2	3.6	
Antagonist	56.8	15.2	
PPOS	39.0	81.3	
E_2 at trigger day (pg/mL)	333 (206.5-559)	495 (265-887.7)	**<0.001**
P at trigger day (ng/mL)	0.3 (0.2-0.4)	6.6 (1.4-12.9)	**<0.001**
Trigger type, n (%)			**<0.001**
hCG	35.6	24.3	
Agonist	22.9	1.7	
Dual	41.5	73.9	
Follicles ≥10 mm at trigger day	2 (1-3)	4 (2-6)	**<0.001**
Oocytes retrieved, n	2 (1-3)	2 (1-5)	**<0.001**
MII oocytes, n	1 (1-2)	2 (0-4)	**0.001**
Oocyte yield (%)[1]	100 (50-100)	73.2 (33.3-100)	0.191
Fertilization rate (%)[2]	50 (0-100) (n=104)	50 (33.3-89.3) (n=98)	0.160
Group-level proportion (%)[3]	67.9% (127/187)	65.3% (186/285)	
Cleavage-stage embryos, n[4]	1 (1-2) (n=72)	2 (1-3) (n=78)	**0.007**
Blastocysts, n[4]	0 (0-0)	0 (0-0)	0.348
Frozen cleavage embryos, n[4]	1 (0-1)	1 (0-2)	**0.005**
Frozen blastocysts, n[4]	0 (0-0)	0 (0-0)	0.348

[1]Oocyte yield = oocytes retrieved/follicles ≥10 mm on trigger day. Calculated only for patients with ≥1 follicle ≥10 mm. [2]Fertilization rate = 2PN zygotes/MII oocytes used for ICSI. Denominator reduced to n=104 (follicular) and n=98 (luteal) because patients with 0 MII oocytes were excluded from the fertilization rate calculation. [3]Fertilization rate: group-level proportions (total 2PN/total MII oocytes). [4]Cleavage embryo number reported only for patients with ≥1 fertilized oocyte (n=72 follicular, n=78 luteal). E_2: Estradiol, P: Progesterone, hCG: Human chorionic gonadotropin, MII: Metaphase II, PPOS: Progestin-primed ovarian stimulation, IQR: Interquartile range, 2PN: Two-pronuclear. Values are mean ± standard deviation or n (%)

Table 3. Transfer outcomes of embryos derived separately from follicular and luteal phase stimulations

	Follicular phase	Luteal phase	Both phases	p
Patients with embryos thawed, n (%) (n=68)	43 (35.8%)	43 (35.8%)	18	
Patients with embryos transferred, n (%) (n=66)	38 (31.7%)	39 (32.5%)	11	
Transferred embryos, n median (IQR)	1 (1-1) (n=38)[1]	1 (1-2) (n=39)[2]		0.157
Implantation rate (%)[3] median (IQR)	0 (0-100) (n=38)	0 (0-50) (n=39)		0.705
Clinical pregnancy rate, % (n)	50.00 (n=19/38)	41.02 (n=16/39)		0.564
Live birth rate, % (n)	23.68 (n=9/38)	33.33 (n=13/39)		0.157

[1]Follicular phase transfers: 30 patients received 1 embryo, 8 received 2 embryos; 5 patients had embryos thawed but not transferred due to poor post-thaw quality. [2]Luteal phase transfers: 22 patients received 1 embryo, 16 received 2 embryos, 1 received 4 embryos; 4 patients had embryos thawed but not transferred due to poor post-thaw quality. [3]Implantation rate = gestational sacs / embryos transferred. Note: 18 patients had embryos from both phases thawed; 11 had transfers from both phases. Transfer outcomes are reported per phase, not per patient. Clinical pregnancy defined as presence of fetal cardiac activity on ultrasound. IQR: Interquartile range

Implantation, clinical pregnancy and live birth rates of embryos derived from the follicular and luteal phases were not statistically significantly different (Table 3).

Initiation day of luteal phase stimulation (oocyte retrieval day/next day vs. ≥2 days after oocyte retrieval) was not found to be associated with clinical pregnancy outcomes (Supplementary Table 1).

Discussion

In this study, which included 120 patients undergoing the DuoStim protocol, luteal phase stimulation yielded a significantly higher number of retrieved oocytes, MII oocytes and frozen cleavage stage embryos compared to follicular phase stimulation. Despite this difference in achieved oocytes, fertilization rates, implantation rates, and clinical pregnancy rates of embryos derived separately from each stimulation phase were comparable between the two phases.

The DuoStim protocol, involving two consecutive ovarian stimulations during the follicular and luteal phases of the same menstrual cycle, was first described by Kuang et al. (6) and is also referred to as the Shanghai protocol. This approach aims to increase the yield of usable oocytes and is particularly useful in cases where a single stimulation is inadequate or when time constraints preclude multiple cycles. As DuoStim minimizes the interval between successive oocyte retrievals, it is especially favored for fertility preservation in patients with medical or social indications (14). In addition, it has been proposed as a viable option for patients with poor ovarian response (7,15).

In our study, both the duration of stimulation and the total gonadotropin dose were higher during follicular phase stimulation. However, contrary findings have been reported, with some studies suggesting that luteal phase stimulation requires a longer duration and higher gonadotropin consumption (5,10). The shorter stimulation duration observed in the luteal phase in our cohort may be attributed to elevated E_2 and P levels. It has been proposed that supraphysiological E_2 and P levels during the luteal phase enhance follicular synchronization and increase the expression of FSH receptors on granulosa cells (16,17). Furthermore, animal studies have demonstrated that high hormonal levels may improve FSH sensitivity of granulosa cells through increased angiogenic factor expression (18). These mechanisms may also contribute to the higher number of oocytes and MII oocytes obtained in the luteal phase in our study.

Our study also revealed comparable fertilization and implantation rates, used as indicators of embryo quality, between follicular and luteal phase stimulations. The BISTIM study which compared DuoStim with two conventional ovarian stimulations in a randomized controlled design, found no difference in reproductive outcomes between the two protocols (19). However, there are few studies comparing the efficiency of follicular and luteal stimulations within the same menstrual cycle, and they have reported conflicting results. While some studies have indicated a diminished response during luteal phase stimulation (4,5), higher oocyte yield during the luteal phase has also been demonstrated (20). In a study by Zhang et al. (21), although stimulation duration and total gonadotropin dose were similar between the two phases, a greater number of oocytes were retrieved during luteal phase stimulation. However, the rate of MII oocytes was lower in the luteal phase, and both cleavage-stage and high-quality embryo rates were comparable between the two phases (21). Cimadomo et al. (16) reported fewer oocyte and blastocyst numbers in follicular phase stimulation. However, pregnancy and delivery rates were similar between follicular phase and luteal phase derived blastocytes (16). In the study of Luo et al. (10), fertilization and frozen embryo rates were similar in both groups, although implantation and pregnancy rates per transfer appeared to be more favorable with embryos derived from luteal phase stimulation. Despite these discrepancies, it has been stated that patients with poor ovarian response who fail to achieve good quality embryos after the first stimulation are more likely to continue stimulation in the same cycle, rather than waiting for a subsequent cycle. As a result, the likelihood of transferring at least one euploid embryo may be higher following a DuoStim protocol compared to two separate conventional stimulations (15). Indeed, previous reports have suggested that DuoStim can increase the number of retrieved oocytes and improve the chance of embryo transfer (2,22,23). Importantly, unlike most published studies that report only oocyte and embryo yield, the present study separately attributes clinical pregnancy outcomes to each stimulation phase, which represents a relatively uncommon approach in the DuoStim literature.

Various stimulation protocols have been described in the literature for both follicular and luteal phases (5,24). In our study, the antagonist protocol was predominantly used during follicular phase stimulation, while the PPOS protocol was more frequently applied in the luteal phase. A previous study employing similar protocols reported no significant differences in embryo quality between the two stimulation phases (10). Also, a recent investigation examining the effects of different follicular phase protocols on subsequent luteal phase outcomes in DuoStim cycles found that both antagonist and PPOS protocols were associated with favorable results with no significant differences (25). Since frozen embryo transfer policies are mandatory in double stimulation cycles, PPOS protocol may present additional advantages in the luteal phase, including lower cost, fewer injections, and prevention of premature menstruation before the second oocyte retrieval.

The choice of trigger was left to the clinician's discretion. Therefore, various trigger protocols including hCG trigger, gonadotropin-releasing hormone (GnRH) agonist trigger and dual

trigger, which combines GnRH agonist with hCG, were utilized in the present study. Dual trigger has been reported to improve the number of oocytes retrieved and enhance reproductive outcomes in patients with poor ovarian response undergoing *in vitro* fertilization (IVF) (17,26), and is often preferred due to these advantages. In the present study, trigger agents were not uniform. Dual trigger was used in 73.9% of luteal phase stimulations and was associated with significantly higher fertilization rates in the luteal phase. The more frequent use of dual trigger at the end of cycles characterized by supraphysiological hormone levels may have further contributed to this finding.

Current literature lacks consensus regarding the optimal interval between oocyte retrieval and initiation of luteal phase stimulation. This interval has been reported to vary from 1 day to 7 days post-retrieval in different studies (3,5,10,24). In a recent large retrospective study, 541 DuoStim cycles were grouped based on the timing of luteal phase stimulation initiation, from 0-2 to 5-6 days, and no significant difference in oocyte yield was found among the groups (27). Consistent with this, no significant differences were observed in our study when luteal phase stimulation was initiated at oocyte retrieval day/next day versus ≥2 days after retrieval (Supplementary Table 1), suggesting flexibility in the application of IVF procedures without strict timing constraints.

Study limitations

The principal strength of this study lies in its reporting of clinical pregnancy rates separately attributable to embryos derived from each stimulation phase within the DuoStim cycle. This approach, which is uncommon in the existing literature, enables a direct comparison of embryo competence between the follicular and luteal phases. The intra-patient design eliminates between-patient confounding, and the cohort of 120 patients represents one of the larger series of this kind reported to date.

However, several limitations of this study merit consideration. First, the retrospective design precludes causal inference, and the non-predefined decision to proceed with luteal phase stimulation introduces substantial selection bias. The decision to initiate luteal phase stimulation was made at oocyte retrieval based on the presence of residual follicular activity on ultrasound, meaning that only patients with at least some remaining follicular potential were included in the DuoStim cohort. This selective inclusion may have favored patients with relatively better ovarian reserve within the poor responder spectrum and may have contributed to the higher oocyte yield observed in the luteal phase.

Second, a formal a priori power calculation was not performed, given the retrospective nature of the study and the limited published data on phase-specific clinical pregnancy rates in DuoStim cycles. This should be considered when interpreting the absence of statistically significant differences in pregnancy outcomes.

Third, stimulation protocols and trigger types differed substantially between follicular and luteal phase stimulations, reflecting routine clinical practice rather than a standardized experimental design. Multivariable adjustment for these protocol differences was not feasible given the sample size. However, given the lack of standardized protocols in the currently limited literature, such variability is not unusual. Finally, embryo transfer was not performed in all patients with frozen embryos, and clinical pregnancy and live birth data were available for only a limited number of patients at the time of analysis.

Conclusion

Our findings indicate that in patients with diminished ovarian reserve undergoing DuoStim, luteal phase stimulation yielded significantly more retrieved oocytes, MII oocytes, and frozen cleavage-stage embryos despite requiring lower gonadotropin doses and shorter stimulation duration. Nevertheless, fertilization rates, implantation rates, and clinical pregnancy rates were comparable between the two phases, suggesting that luteal phase-derived embryos are equally competent to those from the follicular phase. While double stimulation cycles require frozen embryo transfer, luteal phase stimulation appears to be at least as effective as follicular phase stimulation within the same cycle and may contribute to an increased number of transferable embryos in patients with diminished ovarian reserve. Therefore, evaluation of these patients at the end of the follicular phase, with subsequent referral of suitable candidates to a DuoStim protocol, may improve their reproductive outcomes. Further randomized prospective studies are warranted to refine stimulation protocols and evaluate cumulative reproductive outcomes in women with diminished ovarian reserve.

Ethics

Ethics Committee Approval: *This study was performed in line with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the Başkent University where the study was conducted (approval no: KA25/193; date: 19/06/2025).*

Informed Consent: *Informed consent for the use of medical data was obtained from all patients prior to their treatment.*

Footnotes

Author Contributions: *Surgical and Medical Practices: G.D.D., D.A.Y., S.Y., P.Ç.A., E.Ş., Concept: E.Ş., Design: G.D.D., E.Ş., Data Collection or Processing: G.D.D., D.A.Y., S.Y., Analysis or Interpretation: G.D.D., E.Ş., Literature Search: G.D.D., E.Ş., Writing: G.D.D., E.Ş.*

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Supplementary Table 1: *https://d2v96fxpocvxx.cloudfront.net/d87fe3be-5485-41db-ae31-897b8342c583/content-images/29411dad-41ab-4a0c-82db-0f504325cd81.pdf*

References

1. Sighinolfi G, Sunkara SK, La Marca A. New strategies of ovarian stimulation based on the concept of ovarian follicular waves: from conventional to random and double stimulation. Reprod Biomed Online. 2018; 37: 489-97.
2. Gica C, Maxim BG, Botezatu R, Peltecu G, Panaitescu AM, Iordachescu D, et al. Double ovarian stimulation in the same ovarian cycle. Maedica (Bucur). 2021; 16: 102-6.
3. Vaiarelli A, Cimadomo D, Gennarelli G, Guido M, Alviggi C, Conforti A, et al. Second stimulation in the same ovarian cycle: an option to fully-personalize the treatment in poor prognosis patients undergoing PGT-A. J Assist Reprod Genet. 2022; 39: 663-73.
4. Madani T, Hemat M, Arabipoor A, Khodabakhshi SH, Zolfaghari Z. Double mild stimulation and egg collection in the same cycle for management of poor ovarian responders. J Gynecol Obstet Hum Reprod. 2019; 48: 329-33.
5. Bourdon M, Santulli P, Maignien C, Pocate-Cheriet K, Marcellin L, Chen Y, et al. The ovarian response after follicular versus luteal phase stimulation with a double stimulation strategy. Reprod Sci. 2020; 27: 204-10.
6. Kuang Y, Chen Q, Hong Q, Lyu Q, Ai A, Fu Y, et al. Double stimulations during the follicular and luteal phases of poor responders in IVF/ICSI programmes (Shanghai protocol). Reprod Biomed Online. 2014; 29: 684-91.
7. Liu C, Jiang H, Zhang W, Yin H. Double ovarian stimulation during the follicular and luteal phase in women ≥38 years: a retrospective case-control study. Reprod Biomed Online. 2017; 35: 678-84.
8. Ubaldi FM, Capalbo A, Vaiarelli A, Cimadomo D, Colamaria S, Alviggi C, et al. Follicular versus luteal phase ovarian stimulation during the same menstrual cycle (DuoStim) in a reduced ovarian reserve population results in a similar euploid blastocyst formation rate: new insight in ovarian reserve exploitation. Fertil Steril. 2016; 105: 1488-95.
9. Cohen J, Chabbert-Buffet N, Darai E. Diminished ovarian reserve, premature ovarian failure, poor ovarian responder--a plea for universal definitions. J Assist Reprod Genet. 2015; 32: 1709-12.
10. Luo Y, Sun L, Dong M, Zhang X, Huang L, Zhu X, et al. The best execution of the DuoStim strategy (double stimulation in the follicular and luteal phase of the same ovarian cycle) in patients who are poor ovarian responders. Reprod Biol Endocrinol. 2020; 18: 102.
11. Doğan Durdağ G, Çağlar Aytaç P, Alkaş Yağınç D, Yetkinel S, Çok T, Şimşek E. Comparison of fixed and flexible progestin-primed ovarian stimulation protocols to prevent premature luteinization in patients with diminished ovarian reserve. Arch Gynecol Obstet. 2023; 308: 579-86.
12. Gardner DK, Lane M, Stevens J, Schlenker T, Schoolcraft WB. Reprint of: Blastocyst score affects implantation and pregnancy outcome: towards a single blastocyst transfer. Fertil Steril. 2019; 112: e81-e4.
13. Mumusoglu S, Polat M, Ozbek IY, Bozdag G, Papanikolaou EG, Esteves SC, et al. Preparation of the endometrium for frozen embryo transfer: a systematic review. Front Endocrinol (Lausanne). 2021; 12: 688237.
14. Tsampras N, Gould D, Fitzgerald CT. Double ovarian stimulation (DuoStim) protocol for fertility preservation in female oncology patients. Hum Fertil (Camb). 2017; 20: 248-53.
15. Vaiarelli A, Cimadomo D, Conforti A, Schimberni M, Giuliani M, D'Alessandro P, et al. Luteal phase after conventional stimulation in the same ovarian cycle might improve the management of poor responder patients fulfilling the Bologna criteria: a case series. Fertil Steril. 2020; 113: 121-30.
16. Cimadomo D, Vaiarelli A, Colamaria S, Trabucco E, Alviggi C, Venturella R, et al. Luteal phase anovulatory follicles result in the production of competent oocytes: intra-patient paired case-control study comparing follicular versus luteal phase stimulations in the same ovarian cycle. Hum Reprod. 2018; 33: 1442-8.
17. Polat M, Mumusoglu S, Yarali Ozbek I, Bozdag G, Yarali H. Double or dual stimulation in poor ovarian responders: where do we stand? Ther Adv Reprod Health. 2021; 15: 26334941211024172.
18. Macchiarelli G, Jiang JY, Nottola SA, Sato E. Morphological patterns of angiogenesis in ovarian follicle capillary networks. A scanning electron microscopy study of corrosion cast. Microsc Res Tech. 2006; 69: 459-68.
19. Massin N, Abdennebi I, Porcu-Buisson G, Chevalier N, Descat E, Piétin-Vialle C, et al. The BISTIM study: a randomized controlled trial comparing dual ovarian stimulation (duostim) with two conventional ovarian stimulations in poor ovarian responders undergoing IVF. Hum Reprod. 2023; 38: 927-37.
20. Alsbjerg B, Haahr T, Elbaek HO, Laursen R, Povlsen BB, Humaidan P. Dual stimulation using corifollitropin alfa in 54 Bologna criteria poor ovarian responders - a case series. Reprod Biomed Online. 2019; 38: 677-82.
21. Zhang W, Wang M, Wang S, Bao H, Qu Q, Zhang N, et al. Luteal phase ovarian stimulation for poor ovarian responders. JBRA Assist Reprod. 2018; 22: 193-8.
22. Sfakianoudis K, Pantos K, Grigoriadis S, Rapani A, Maziotis E, Tsioulou P, et al. What is the true place of a double stimulation and double oocyte retrieval in the same cycle for patients diagnosed with poor ovarian reserve? A systematic review including a meta-analytical approach. J Assist Reprod Genet. 2020; 37: 181-204.
23. Majumdar A, Majumdar G, Tiwari N, Singh A, Gupta SM, Satwik R. Luteal phase stimulation in the same cycle is an effective strategy to rescue POSEIDON poor responders with no embryos after the first follicular stimulation. J Hum Reprod Sci. 2023; 16: 218-26.
24. Li J, Lyu S, Lyu S, Gao M. Pregnancy outcomes in double stimulation versus two consecutive mild stimulations for IVF in poor ovarian responders. J Clin Med. 2022; 11: 6780.
25. Chen Y, Ye H, Bao J, Cai Y, Hu Y, Yan H. Retrospective study of influencing factors on the outcomes of luteal phase stimulation in patients with dual stimulation. Peer J. 2023; 11: e15296.
26. Chern CU, Li JY, Tsui KH, Wang PH, Wen ZH, Lin LT. Dual-trigger improves the outcomes of in vitro fertilization cycles in older patients with diminished ovarian reserve: a retrospective cohort study. PLoS One. 2020; 15: e0235707.
27. Fuentes A, García-Ajofrín C, Romero R, Castillo JC, Ortíz JA, Hortal M, et al. Influence of the starting day of luteal phase stimulation on double stimulation cycles. Front Endocrinol (Lausanne). 2023; 14: 1216671.

Evaluation of angiopoietin-like protein 4 levels in patients with endometriosis

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Abstract

Objective: Endometriosis is a chronic inflammatory disorder lacking definitive laboratory diagnostic markers. Angiopoietin-like protein-4 (ANGPTL4) is a protein involved in the regulation of angiogenesis and inflammation. The aim of the present study was to evaluate serum and peritoneal fluid (PF) levels of ANGPTL4 to explore its potential role in the pathogenesis of endometriosis.

Material and Methods: This prospective study included women with surgically confirmed endometriosis and age-matched healthy controls with similar demographic characteristics. Clinical and laboratory parameters, including serum ANGPTL4, anti-Müllerian hormone (AMH), and cancer antigen-125 (CA125) levels were compared between groups. In addition, PF ANGPTL4 levels were assessed in the endometriosis group.

Results: Serum ANGPTL4 (512.65±46.91 vs. 177.60±11.84 ng/mL, $p<0.001$) and CA125 (53.52±6.05 vs. 20.10±3.18 U/mL, $p<0.001$) levels were significantly higher in endometriosis group. Serum ANGPTL4 positively correlated with the severity of pelvic pain and dyspareunia, serum CA125 level and PF ANGPTL4, and negatively correlated with AMH ($r=0.743$, $p<0.001$; $r=0.624$, $p<0.001$; $r=0.444$, $p<0.001$; $r=0.841$, $p<0.001$; and $r=-0.380$, $p<0.001$, respectively). Receiver operating characteristic analysis identified an optimal serum ANGPTL4 cut-off value of 188.61 ng/mL (area under the curve =0.755, sensitivity 75% and specificity 62.5%, positive predictive value 66.7%, and negative predictive value 71.4%).

Conclusion: Serum ANGPTL4 levels were significantly higher in women with endometriosis and were associated with clinical and laboratory parameters. It may serve as a supportive biomarker in the clinical assessment of endometriosis. [J Turk Ger Gynecol Assoc. 2026; 27(3): 203-10]

Keywords: Anti-Müllerian hormone, angiopoietin-like protein 4, CA125 antigen, endometriosis, pelvic pain

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Introduction

Endometriosis is a chronic, progressive disease characterized by local and systemic inflammation and the presence of ectopic endometrial tissue (1,2). Ectopic endometrial implants are most frequently observed in the ovaries, as well as in extraovarian pelvic peritoneal locations, including the broad ligament, pouch of Douglas, and uterosacral ligaments (2,3). Endometriosis is clinically diagnosed in approximately 10% of women of reproductive age. Its most common manifestations include infertility and pain-related symptoms, particularly dysmenorrhea and chronic pelvic pain, which have been shown to markedly reduce quality of life (1,2).

Currently, no biomarker has demonstrated sufficient accuracy to serve as a standalone diagnostic tool for endometriosis (4). The clinical value of cancer antigen-125 (CA125) for diagnosing endometriosis is restricted because elevated levels can occur in ovarian, bladder, and renal cancers, as well as in inflammatory disorders and adenomyosis (5). Surgery remains the gold standard for the diagnosis of endometriosis (3). Therefore, research efforts have increasingly focused on developing non-invasive diagnostic methods suitable for clinical use.

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Although the pathogenesis of endometriosis has not been fully elucidated, angiogenesis, inflammation, oxidative stress, and fibrosis are recognized as central mechanisms (2). Angiopoietin-like protein 4 (ANGPTL4), a member of the angiopoietin-like family, is involved in the regulation of inflammation and angiogenesis (6). However, the role of ANGPTL4 in the pathophysiology and clinical significance of endometriosis remains insufficiently understood. The revised American Society for Reproductive Medicine (rASRM) classification is the most widely used surgical staging system for endometriosis and remains the standard method for assessing disease extent despite its limited correlation with symptom severity (7,8). Whether circulating and local ANGPTL4 levels vary according to disease stage has not yet been investigated. Given this context, the current study aimed to investigate whether serum levels of ANGPTL4 may have potential value in the clinical evaluation of women with endometriosis compared with a healthy control group. In addition, peritoneal fluid (PF) ANGPTL4 levels were evaluated in the endometriosis group for a better understanding of local factors. Furthermore, serum and PF ANGPTL4 levels were evaluated according to rASRM stage to explore their association with disease severity.

Material and Methods

Study population

The study was approved by Ankara Bilkent City Hospital Ethics Committee (approval no: TABED 1-25-1372, date: 04.06.2025) and National Institutes of Health Clinical Trial's Registry (#NCT07164196).

After detailed information about the study protocol was provided, written informed consent was obtained from all participants.

Exclusion criteria for both the endometriosis and control groups included postmenopausal status, a history of previous surgery for endometriosis, adenomyosis, infectious or acute/chronic inflammatory diseases, autoimmune disorders, tumor history, menorrhagia or hypermenorrhea, pregnancy, lactation, use of intrauterine devices, and any medical treatment, including hormonal therapy or antidiabetic medications.

Data collection and evaluation of ANGPTL4 levels

Demographic characteristics and clinical findings, including body mass index (BMI), serum CA125 levels, serum anti-Müllerian hormone (AMH) levels, pelvic pain, and dyspareunia were recorded for all participants. Serum ANGPTL4 levels were compared between the endometriosis patients and the healthy controls. The PF ANGPTL4 levels were also evaluated, but only in women with endometriosis.

Dyspareunia was defined as recurrent or persistent pain associated with sexual intercourse which causes distress, including the complaints during or within 24 hours after the intercourse (9). Pelvic pain was defined as cyclic or non-cyclic lower abdominal pain for at least six months, unrelated to pregnancy (10). Visual analogue scale (VAS) for pain, with possible scores from 0 to 10, was applied to investigate the presence and severity of both pelvic pain and dyspareunia. The 0 point was assessed as having no pain, whereas the 10 point was assigned to the worst pain the patient had experienced (11).

The blood serum was analyzed to observe systemic ANGPTL4 levels, and the PF was analyzed for the local ANGPTL4 levels in pelvic peritoneum. Blood sampling from antecubital vein after eight hours fasting was performed to obtain serum samples. The PF samples were taken at the begining of the laparoscopic procedure just after the insertion of the first lateral trochar into the peritoneal cavity. The peripheral venous blood serum and PF samples were centrifuged at 2500 rpm for 15 min. All the collected samples were stored at -80 °C in aliquots and the ANGPTL4 levels were analyzed at once. The ANGPTL4 levels were determined using an enzyme-linked immunosorbent assay (ELISA) kit (catalog no. E3119Hu/Bioassay Technology Laboratory, Shanghai, China) by quantitative sandwich ELISA. The absorbance values were read at 450 nm using Thermo Scientific Multiskan GO spectrophotometer (Thermo Fisher Scientific, USA). The assay sensitivity (minimum detectable concentration) was 12.5 ng/mL. The intra-assay and inter-assay coefficients of variation (CVs) were <10%.

Statistical analysis

Statistical Package for the Social Sciences, v27.0 for Windows (SPSS Inc., Chicago, IL, USA) was used in statistical analyses. Categorical variables were compared using Pearson's chi-square test. Fisher's exact test was used when the assumptions for the chi-square test were not met. The normality of continuous variables was assessed using the Shapiro-Wilk test. Normally distributed continuous variables are expressed as mean ± standard deviation and compared using Student's t-test, whereas non-normally distributed variables are expressed as median (minimum-maximum) and analyzed using the Mann-Whitney U test. A post-hoc power analysis was performed using G*Power version 3.1 (Heinrich Heine University, Düsseldorf, Germany) for the primary outcome (serum ANGPTL4 levels) based on a two-tailed independent samples t-test. The analysis assumed an effect size of Cohen's d=1.8, an alpha level of 0.05, and the observed group sizes (n=40 per group). The achieved statistical power was >0.99.

Spearman's rank correlation analysis was performed to assess the relationships between serum and PFANGPTL4 levels and

clinical and biochemical variables. Furthermore, to determine whether ANGPTL4 levels were independently associated with disease severity after adjustment for potential confounding factors, separate multivariable linear regression analyses were performed for serum and PFANGPTL4 levels in the endometriosis group. Patients with endometriosis were further stratified according to rASRM stage (stage III and stage IV), and serum and PFANGPTL4 levels were compared between the two groups. Disease stage (rASRM), infertility, serum AMH, and serum CA125 were entered simultaneously into the models using the enter method. Multicollinearity was assessed using variance inflation factors, and values <2 were considered indicative of the absence of significant multicollinearity.

To evaluate whether serum ANGPTL4 was independently associated with the presence of endometriosis, a multivariable binary logistic regression analysis was performed with endometriosis status (case/control) as the dependent variable. Serum ANGPTL4, serum CA125, serum AMH, and infertility status were entered simultaneously as independent variables using the enter method. These covariates were selected based on their clinical relevance and their potential to confound the association between serum ANGPTL4 and the presence of endometriosis. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Model calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test.

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of serum ANGPTL4, and the area under the curve (AUC), optimal cut-off value, sensitivity, and specificity were determined. To evaluate the incremental diagnostic value of serum ANGPTL4 beyond CA125, a binary logistic regression model was constructed with endometriosis status as the dependent variable and serum CA125 and serum ANGPTL4 levels as independent variables. Predicted probabilities from this model were used to generate the combined CA125-ANGPTL4 ROC curve. ROC curves were also generated separately for serum CA125 and serum ANGPTL4. The AUCs and their 95% CIs were calculated, and the AUC of the combined model was compared with that of CA125 alone using the non-parametric DeLong test for correlated ROC curves. A p-value of <0.05 was considered statistically significant.

Results

A total of 92 women of reproductive age were enrolled. After the relevant exclusions as shown in the flow diagram (Figure 1), 80 participants remained in final analysis, consisting of 40 women who underwent laparoscopic surgery and received a confirmed diagnosis of endometriosis and the control group of 40 women. Clinical characteristics, demographic data and ANGPTL4 levels are shown in Table 1. Serum ANGPTL4, CA125 levels, pelvic pain scores, and dyspareunia scores were significantly increased in the endometriosis group ($p<0.001$), whereas serum AMH levels were significantly decreased in the endometriosis group ($p<0.001$) (Table 1).

Spearman's correlation analysis revealed significant and strong association between the serum and PF levels of ANGPTL4 ($r=0.841$, $p<0.001$). Serum AMH levels were negatively correlated with serum and PF ANGPTL4 levels and with serum CA125 levels ($r=-0.380$, $p<0.001$; $r=-0.370$, $p=0.019$; $r=-0.298$, $p=0.007$, respectively). ANGPTL4 levels were significantly correlated with serum CA125 levels, as well as with pelvic pain and dyspareunia VAS scores ($p<0.05$), as presented in Table 2.

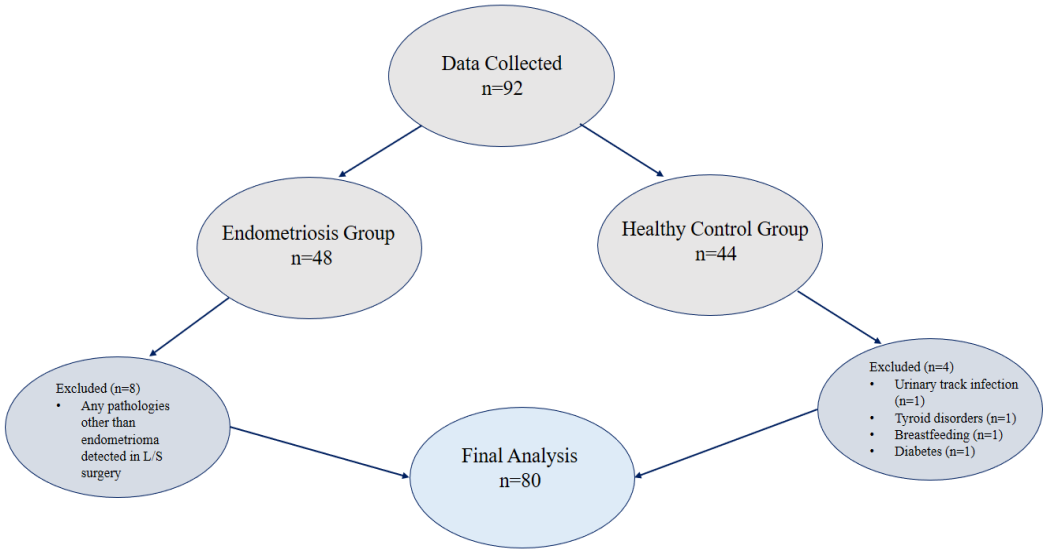

Figure 1. Flow diagram of the study
L/S surgery: Laparoscopic surgery

A multivariable binary logistic regression analysis was performed to determine whether serum ANGPTL4 was independently associated with the presence of endometriosis after adjustment for serum CA125, serum AMH, and infertility status. The overall model was significant (Omnibus test, χ^2=57.906, p<0.001) and demonstrated good calibration (Hosmer-Lemeshow test, χ^2=10.215, p=0.250). The Nagelkerke R^2 was 0.687. Serum ANGPTL4 was not independently associated with endometriosis after adjustment for serum CA125, serum AMH, and infertility status (adjusted OR =1.003, 95% CI: 0.998-1.009, p=0.235), whereas serum CA125 was the only variable that remained significantly associated with endometriosis (adjusted OR=1.081, 95% CI: 1.017-1.148, p=0.012).

The ROC analysis demonstrated that serum ANGPTL4 had a statistically significant ability to discriminate women with endometriosis from controls (AUC =0.755, 95% CI: 0.648-0.862; p<0.001). At the optimal cut-off value of 188.61 ng/mL, serum ANGPTL4 showed a sensitivity of 75% and a specificity of 62.5%, with a positive predictive value of 66.7% and a negative predictive value of 71.4% (Table 3). Serum CA125 also demonstrated significant discriminatory ability for endometriosis, with an AUC of 0.888 (95% CI, 0.815-0.962; p<0.001). To further evaluate the incremental diagnostic value of serum ANGPTL4 beyond CA125, a combined model incorporating serum CA125 and serum ANGPTL4 was evaluated. The combined model demonstrated a higher AUC of 0.931 (95% CI, 0.879-0.982; p<0.001) than CA125 alone. The difference between the AUCs of serum CA125 alone and the combined CA125-ANGPTL4 model was statistically significant according by the DeLong test (difference in AUC, 0.051; 95% CI, 0.003-0.099; p=0.037), indicating significantly improved discriminatory performance with the addition of serum ANGPTL4. The ROC characteristics of the individual biomarkers and the combined model are presented in Table 3 and Figure 2.

Table 1. Sociodemographic characteristics and clinical findings of the participants

	Endometriosis group (n=40)	Control group (n=40)	p-value
Age† years	33.72±1.05	36.19±1.19	0.624
BMI† kg/m²	25.95±0.89	25.08±1.64	0.628
Pelvic pain VAS‡ 0-10 points	6 (3-8)	2 (2)	<0.001*
Dyspareunia VAS‡ 0-10 points	4 (3-7)	2 (2.25)	<0.001*
AMH† ng/mL	1.39±0.23	1.81±0.42	<0.001*
Serum CA125† U/mL	53.52±6.05	20.10±3.18	<0.001*
ANGPTL4 serum† ng/mL	512.65±46.91	177.60±11.84	<0.001*
ANGPTL4 PF ng/mL	314.76±15.17	N/A	N/A

*p-value <0.05 is considered as statistically significant. †: Student's t-test, ‡: Mann-Whitney U test. ANGPTL4 PF levels were measured only in the endometriosis group. N/A: Non-applicable, BMI: Body mass index, VAS: Visual analogue scale, AMH: Anti-Müllerian hormone, CA125: Cancer antigen-125, ANGPTL4: Angiopoietin-like protein-4, PF: Peritoneal fluid

Table 2. Correlation analysis between ANGPTL4 levels and clinical and laboratory parameters in women with endometriosis

		ANGPTL4 PF	ANGPTL4 serum	Dyspareunia	Pelvic pain	AMH	CA125
CA125	r	0.387	0.444	0.588	0.594	-0.298	N/A
	p-value	0.014*	<0.001*	<0.001*	<0.001*	0.007*	N/A
AMH	r	-0.370	-0.380	-0.509	-0.399	N/A	
	p-value	0.019*	<0.001*	<0.001*	<0.001*	N/A	
Pelvic pain	r	0.548	0.743	0.764	N/A		
	p-value	<0.001*	<0.001*	<0.001*	N/A		
Dyspareunia	r	0.452	0.624	N/A			
	p-value	0.004*	<0.001*	N/A			
ANGPTL4 serum	r	0.841	N/A				
	p-value	<0.001*	N/A				
ANGPTL4 PF	r	N/A					
	p-value	N/A					

*p-value <0.05 is considered as statistically significant. N/A: Non-applicable, AMH: Anti-Müllerian hormone, CA125: Cancer antigen-125, ANGPTL4: Angiopoietin-like protein-4, PF: Peritoneal fluid

Serum and PF ANGPTL4 levels were significantly higher in women with stage IV endometriosis (n=23) than in those with stage III disease (n=17) (serum: 761.26±497.05 vs. 369.16±234.20 ng/mL, p=0.026; PF: 334.38±89.25 vs. 277.09±64.19 ng/mL, p=0.034). Multivariable linear regression analyses demonstrated that disease stage was independently associated with both serum and PF ANGPTL4 levels, whereas infertility, serum AMH, and serum CA125 were not independent predictors (Table 4).

Table 3. Diagnostic performance of serum CA125, serum ANGPTL4, and the combined CA125-ANGPTL4 model for the diagnosis of endometriosis

	AUC	SE	p-value	95% CI	Optimal cut-off value	Sensitivity (%)	Specificity (%)
CA125	0.888	0.037	<0.001*	0.815-0.962	16.30	85	72.5
Serum ANGPTL4	0.755	0.055	<0.001*	0.648-0.862	188.61	75	62.5
CA125 and serum ANGPTL4	0.931	0.026	<0.001*	0.879-0.982	-	-	-

*p-value <0.05 is considered as statistically significant. AUC: Area under curve, SE: Standard Error, CI: Confidence interval, CA125: Cancer antigen-125, ANGPTL4: Angiopoietin-like protein-4

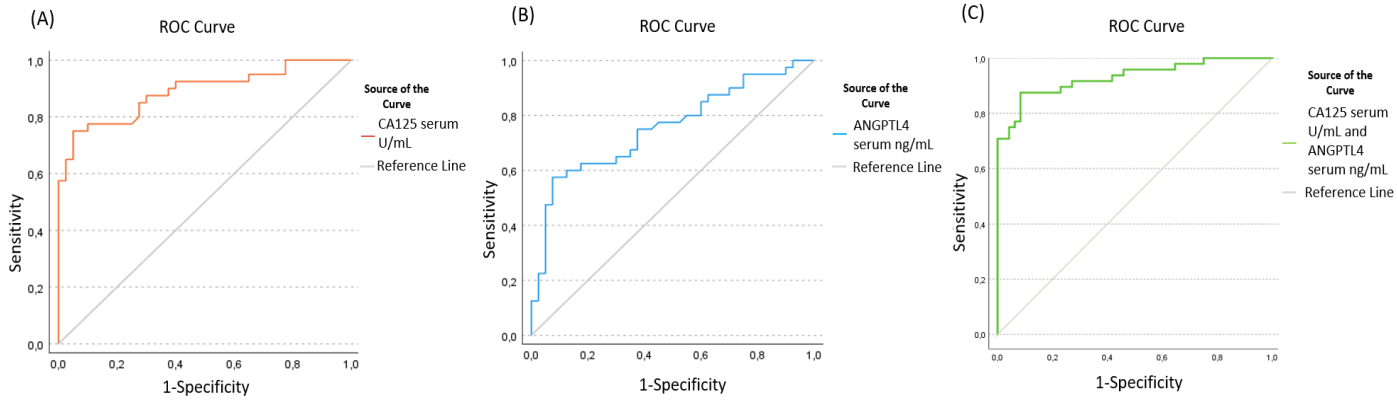

Figure 2. The ROC curves of serum CA125 (A), ANGPTL4 levels (B) and the combined serum CA125-ANGPTL4 (C) in endometriosis diasease

ROC: Receiver operating characteristic, CA125: Cancer antigen-125, ANGPTL4: Angiopoietin-like protein-4

Table 4. Multivariable regression analyses for serum and peritoneal fluid ANGPTL4 in the endometriosis group

Dependent variable	R^2-adjusted R^2	p-value	B (95% CI)	Independent predictors coefficients (standardized β)	p-value
Serum ANGPTL4, ng/mL	0.415-0.348	0.001*			
Disease stage (rASRM)			325.94 (88.07 to 563.81)	0.365	0.009*
Infertility			198.06 (-91.82 to 487.93)	0.219	0.174
Serum AMH, ng/mL			-54.89 (-172.69 to 62.92)	-0.151	0.351
Serum CA125, U/mL			0.77 (-0.17 to 1.71)	0.238	0.104
PF ANGPTL4, ng/mL	0.365-0.293	0.003*			
Disease stage (rASRM)			44.92 (1.40 to 91.24)	0.269	0.047*
Infertility			50.53 (-5.92 to 106.98)	0.299	0.078
Serum AMH, ng/mL			-4.73 (-27.67 to 18.21)	-0.070	0.678
Serum CA125, U/mL			0.16 (-0.03 to 0.34)	0.258	0.090

*p-value <0.05 is considered as statistically significant. Multivariable linear regression analyses were performed using the enter method. Standardized β coefficients and p-values are shown. Independent variables included disease stage (according to rASRM classification), infertility, serum AMH, and CA125. Variance inflation factors were <2 for all models, indicating no significant multicollinearity. ANGPTL4: Angiopoietin-like protein-4, rASRM: Revised American Society for Reproductive Medicine, AMH: Anti-Müllerian hormone, CA125: Cancer antigen-125, PF: Peritoneal fluid, CI: Confidence interval

Discussion

In the present study, women with endometriosis exhibited significantly higher serum ANGPTL4 levels compared with healthy controls. Serum ANGPTL4 levels were positively correlated with pelvic pain, dyspareunia, serum CA125 levels, and PFANGPTL4 concentrations, while showing a negative correlation with AMH levels. Furthermore, serum ANGPTL4 demonstrated a moderate ability to discriminate women with endometriosis from controls. Endometriosis is associated with a proinflammatory condition characterized by the presence of ectopic endometrial tissue (1,2). In the literature, ANGPTL4 was reported to contribute to vascular permeability, angiogenesis, and various immune pathways (12). The expression and secretion of ANGPTL4 have been closely linked to chronic inflammatory processes and macrophage-mediated immune responses so that ANGPTL4 is upregulated in response to inflammatory macrophages and modulates their phenotype in pathological conditions (6,13). Its expression has also been found to correlate with increases in pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-6, suggesting that inflammatory signaling promotes ANGPTL4 expression, while anti-inflammatory pathways may oppose this effect (13). Previous studies have indicated that TNF-α and interferon-gamma play key roles in promoting the inflammatory response underlying the etiopathogenesis of endometriosis (14,15). However, to the best of our knowledge, the present study is the first to evaluate serum and/or PF ANGPTL4 levels in women with endometriosis. In our study, women with endometriosis demonstrated significantly elevated ANGPTL4 levels, and serum ANGPTL4 emerged as a potential discriminative biomarker for the disease. Although the discriminatory performance of serum ANGPTL4 alone was moderate (AUC =0.755), this finding suggests that ANGPTL4 may contribute to the clinical assessment of endometriosis rather than serving as a standalone diagnostic marker. Consistent with prior evidence, this novel observation appears biologically plausible and aligns with the inflammatory pathophysiology of the disease.

An additional finding of the present study was that both serum and PF ANGPTL4 levels were significantly higher in women with stage IV endometriosis than in those with stage III disease. Previous studies have shown that rASRM staging does not consistently correlate with symptom severity or clinical manifestations of endometriosis, and its ability to reflect disease burden remains limited (16). Similarly, CA125 has been shown to have limited value in accurately reflecting disease stage or severity (17). More broadly, biomarker studies in endometriosis have demonstrated significant heterogeneity in their association with disease severity, and no single biomarker has shown consistent performance across disease stages (18). In this context, multivariable modeling approaches are recommended to account for confounding clinical and hormonal factors when evaluating candidate biomarkers (18). Taken together, the present findings suggest that ANGPTL4 may be associated with both inflammatory activity and disease severity in endometriosis.

ANGPTL4 has been associated with gynecological conditions characterized by metabolic and inflammatory dysregulation, such as polycystic ovary syndrome, with increased expression in ovarian granulosa cells reported in affected women (19). In the current study, serum ANGPTL4 levels were also found to distinguish women with endometriosis from healthy controls. Cytokines present in the PF of women with endometriosis have been reported to directly enhance endometrial cell proliferation, invasion, and neovascularization, thereby facilitating lesion progression (20). Moreover, impaired clearance of endometrial cells by macrophages and natural killer cells may exacerbate abnormal cytokine production, sustaining peritoneal inflammation in endometriosis patients (18). The detection of ANGPTL4 in the PF of women with endometriosis may be clinically relevant, as it likely reflects local pelvic peritoneal inflammation. Furthermore, the significant correlation observed between serum and PF ANGPTL4 levels indicates that circulating ANGPTL4 may represent a non-invasive surrogate marker of pelvic inflammatory activity. Taken together, these findings suggest that serum ANGPTL4 may provide insight into both local and systemic inflammatory processes in endometriosis. The observed sensitivity and specificity further support its potential applicability as a biomarker in the clinical evaluation of the disease.

CA125, a recognized inflammatory marker, has been shown to increase in women with endometriosis (5). However, due to its limited specificity, recent studies have suggested that discovering new biomarkers will be important to enhance diagnostic accuracy in endometriosis (5). Consistent with previous studies, in the current study, serum CA125 levels were elevated in the endometriosis group. The alignment of our diagnostic sensitivity and specificity results with those reported in the literature (5) further supports the validity of our study population in representing endometriosis cases. Serum CA125, a widely used clinical marker in the evaluation of endometriosis, showed a significant correlation with both systemic and local ANGPTL4 levels. This association between ANGPTL4 and CA125 is particularly noteworthy, as it further reinforces the potential role of serum ANGPTL4 as a supportive biomarker in the clinical assessment of endometriosis.

After adjustment for relevant clinical and laboratory variables, serum ANGPTL4 was not independently associated with the presence of endometriosis. This finding suggests that the association between serum ANGPTL4 levels and endometriosis may be influenced by other clinical or biochemical factors.

An important finding of the present study is that the diagnostic performance of serum ANGPTL4 was not limited to its performance as an individual biomarker. When serum ANGPTL4 was incorporated into a multivariable logistic regression model with CA125, the resulting combined model demonstrated a higher discriminatory capacity than CA125 alone. Importantly, this improvement was statistically significant according to the DeLong test, supporting an incremental diagnostic contribution of serum ANGPTL4 beyond CA125. These findings suggest that serum ANGPTL4 may provide complementary diagnostic information to CA125 rather than simply representing an alternative biomarker. However, the clinical relevance of this combined diagnostic approach remains to be established.

Pain represents one of the most distressing symptoms in endometriosis. The complex interplay of elevated PF cytokines and chemokines has been implicated in driving both pelvic pain and dyspareunia (21). Notably, interleukin-8 and TNF-α are among key pro-inflammatory cytokines implicated in the pathophysiology of endometriosis. These mediators are associated with enhanced local inflammation, immune cell activation, and lesion development, which contribute to pain and disease progression. Pro-inflammatory signaling and cytokine dysregulation remain central features of endometriosis pathobiology (20,22). Women with endometriosis in this study reported higher VAS scores for pelvic pain and dyspareunia. ANGPTL4 levels were positively associated with the severity of pelvic pain and dyspareunia, and both serum and PF ANGPTL4 concentrations significantly correlated with pain severity. These observations constitute novel findings, highlighting a potential role of ANGPTL4 in the pathophysiology of endometriosis-associated pain. Considering the proinflammatory milieu in endometriosis at both local and systemic levels (2,20), the correlations between ANGPTL4, serum CA125 levels, and the severity of pelvic pain and dyspareunia are pathophysiologically consistent. These findings suggest that both systemic and local ANGPTL4 levels may have value in reflecting the clinical relevance of endometriosis-associated pain. Evaluation of ANGPTL4 in conjunction with pain-related cytokines and chemokines at both systemic and local levels may provide further clarification of this relationship in women with endometriosis. Furthermore, better understanding of ANGPTL4-related pathways may also contribute to improvement in therapeutic approaches targeting inflammation-associated pain.

Endometriosis has been linked to reduced ovarian reserve and impaired fertility, resulting from either the inflammatory milieu created by endometriotic foci or surgical treatment of lesions (23). AMH, produced by granulosa cells of small growing ovarian follicles, serves as a reliable biomarker for assessing the functional ovarian reserve and reflects the remaining follicular pool, making it a key early indicator of diminished ovarian function (24). Previous studies have reported decreased serum AMH levels in women with endometriosis, as well as an inverse correlation between serum CA125 and AMH levels (25). In line with previous evidence, women with endometriosis in this study had reduced serum AMH levels, which negatively correlated with serum CA125. Notably, given the reported inhibitory effects of ANGPTL4 on granulosa cell proliferation (26), our results demonstrated an inverse relationship between serum AMH and ANGPTL4 levels in both serum and PF, representing a novel finding of this study. Collectively, these findings support a potential association between inflammatory activity and ovarian reserve in endometriosis-related infertility.

Study limitations

The present study has several strengths and limitations that warrant consideration. A major strength is the definitive diagnosis of endometriosis confirmed by laparoscopy, together with the opportunity to assess local ANGPTL4 levels through PF sampling obtained during surgery. However, the invasive nature of PF collection limited the inclusion of healthy control samples. Given that AMH levels are known to decline with advancing age, higher BMI, and a history of prior ovarian surgery (23,27), the comparability of the study groups with respect to these variables further strengthens the validity of our findings.

The observed associations between ANGPTL4 levels, pain severity, CA125, and ovarian reserve markers suggest a potential role for ANGPTL4 in the clinical evaluation of women with endometriosis. In addition to reflecting inflammatory activity, its assessment alongside established clinical and laboratory parameters may provide complementary information regarding disease-related manifestations. Moreover, evaluating ANGPTL4 in conjunction with other inflammatory mediators may contribute to a better understanding of the biological mechanisms underlying endometriosis and its potential clinical applicability.

Conclusion

Inflammatory mechanisms play a central role in the pathogenesis of endometriosis, and accumulating evidence highlights the contribution of immune dysregulation to disease development. In line with this concept, the present study identifies ANGPTL4 as a potential mediator of the aberrant inflammatory response observed in endometriosis. These findings should be interpreted in the context of the study design and population characteristics. The significant correlation between serum and PF ANGPTL4 levels indicates that circulating ANGPTL4 may reflect local inflammatory activity. Taken together, the associations between ANGPTL4, clinical manifestations, and CA125 levels highlight its potential utility as a supportive clinical biomarker in the evaluation of women with endometriosis.

Ethics

Ethics Committee Approval: *The study was approved by Ankara Bilkent City Hospital Ethics Committee (approval no: TABED 1-25-1372, date: 04.06.2025) and National Institutes of Health Clinical Trial's Registry (#NCT07164196).*

Informed Consent: *Written informed consent was obtained from all participants.*

Footnotes

Author Contributions: *Surgical and Medical Practices: M.D.E.T., E.M.E.K., Concept: M.D.E.T., Design: M.D.E.T., E.M.E.K., Data Collection or Processing: M.D.E.T., Analysis or Interpretation: E.M.E.K., Literature Search: M.D.E.T., Writing: M.D.E.T., E.M.E.K.*

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References

1. Pašalić E, Tambuwala MM, Hromić-Jahjefendić A. Endometriosis: classification, pathophysiology, and treatment options. Pathol Res Pract. 2023; 251: 154847.
2. Simancas-Racines D, Jiménez-Flores E, Montalvan M, Horowitz R, Araujo V, Reytor-González C. Endometriosis as a systemic and complex disease: toward phenotype-based classification and personalized therapy. Int J Mol Sci. 2026; 27: 908.
3. Freger SM, Marien M, Mick I, Leonardi M. Anatomical distribution of ovarian and deep endometriosis using a multimodal diagnostic approach applying the updated international definition: a prospective observational study. Eur J Obstet Gynecol Reprod Biol. 2026; 318: 114947.
4. Nisenblat V, Bossuyt PM, Shaikh R, Farquhar C, Jordan V, Scheffers CS, et al. Blood biomarkers for the non-invasive diagnosis of endometriosis. Cochrane Database Syst Rev. 2016; 2016: CD012179.
5. Wu L, Yang Z, Chen H, Piao Y. Diagnostic accuracy of combination of CA125 for endometriosis: a network meta-analysis. Int J Gynaecol Obstet. 2026; 172: 1342-55.
6. Zuo Y, He Z, Chen Y, Dai L. Dual role of ANGPTL4 in inflammation. Inflamm Res. 2023; 72: 1303-13.
7. Manu A, Poenaru E, Duica F, Bausic AIG, Coroleuca BC, Coroleuca CA, et al. Quality of life assessment and clinical implications for women with endometriosis through validated tools: a narrative review. Medicina (Kaunas). 2025; 61: 1729.
8. Hudelist G, Valentin L, Saridogan E, Condous G, Malzoni M, Roman H, et al. What to choose and why to use - a critical review on the clinical relevance of rASRM, EFI and Enzian classifications of endometriosis. Facts Views Vis Obgyn. 2021; 13: 331-8.
9. Rahmawati NY, Ahsan F, Santoso B, Mufid AF, Sa'adi A, Dwiningsih SR, et al. IL-8 and IL-12p70 are associated with pelvic pain among infertile women with endometriosis. Pain Med. 2023; 24: 1262-9.
10. Gin GT, Rosenblum E, Wilkinson LD, Brady PH. Female pelvic conditions: chronic pelvic pain. FP Essent. 2022; 515: 11-9.
11. Modarresi S, Lukacs MJ, Ghodrati M, Salim S, MacDermid JC, Walton DM, et al. A systematic review and synthesis of psychometric properties of the numeric pain rating scale and the visual analog scale for use in people with neck pain. Clin J Pain. 2021; 38: 132-48.
12. Giacomini E, Minetto S, Li Piani L, Pagliardini L, Somigliana E, Viganò P. Genetics and inflammation in endometriosis: improving knowledge for development of new pharmacological strategies. Int J Mol Sci. 2021; 22: 9033.
13. Górecka M, Krzemiński K, Mikulski T, Ziemba AW. ANGPTL4, IL-6 and TNF-α as regulators of lipid metabolism during a marathon run. Sci Rep. 2022; 12: 19940.
14. Karakoç E, Halaçlı SO, Hanelçi RH, Ayhan S, Eylem CC, Nemutlu E, et al. N-acetylcysteine stimulates organelle malfunction in endometriotic cells via IFN-gamma signaling. Sci Rep. 2025; 15: 15120.
15. Chang LY, Shan J, Hou XX, Li DJ, Wang XQ. Synergy between Th1 and Th2 responses during endometriosis: a review of current understanding. J Reprod Immunol. 2023; 158: 103975.
16. Horne AW, Missmer SA. Pathophysiology, diagnosis, and management of endometriosis. BMJ. 2022; 379: e070750.
17. Feduniw S, Pruc M, Ciebiera M, Safiejko K, Bizon M, Szarpak L. Current evidence on CA125 levels in differentiation between endometriomas and endometriosis-associated ovarian cancer - a systematic review and meta-analysis. J Endometr Pelvic Pain Disord. 2024; 16: 154-9.
18. Chen S, Liu Y, Zhong Z, Wei C, Liu Y, Zhu X. Peritoneal immune microenvironment of endometriosis: Role and therapeutic perspectives. Front Immunol. 2023; 14: 1134663.
19. Jiang Q, Pan Y, Li P, Zheng Y, Bian Y, Wang W, et al. ANGPTL4 expression in ovarian granulosa cells is associated with polycystic ovary syndrome. Front Endocrinol (Lausanne). 2021; 12: 799833.
20. Oală IE, Mitranovici MI, Chiorean DM, Irimia T, Crișan AI, Melinte IM, et al. Endometriosis and the role of pro-inflammatory and anti-inflammatory cytokines in pathophysiology: a narrative review of the literature. Diagnostics (Basel). 2024; 14: 312.
21. Malvezzi H, Hernandes C, Piccinato CA, Podgaec S. Interleukin in endometriosis-associated infertility-pelvic pain: systematic review and meta-analysis. Reproduction. 2019; 158: 1-12.
22. Makoui MH, Fekri S, Makoui RH, Ansari N, Esmaeilzadeh A. The role of mast cells in the development and advancement of endometriosis. Am J Reprod Immunol. 2025; 93: e70019.
23. Ramezani Tehrani F, Mousavi M, Noori Ardebili S, Saei Ghare Naz M, Azizi F, Behboudi-Gandevani S. Association between anti-Mullerian hormone levels and age in women with endometriosis: insights from a population-based study. BMJ Open. 2025; 15: e102774.
24. Moolhuijsen LME, Visser JA. Anti-Müllerian hormone and ovarian reserve: update on assessing ovarian function. J Clin Endocrinol Metab. 2020; 105: 3361-73.
25. Lan S, Wang X, Cui P, Wang C, Zhai M, Li Y, et al. A real-world study of changes in preoperative and postoperative CA125, A and MH in patients with endometriosis. Front Med Sci Res. 2022; 4: 41-6.
26. Jiang Q, Miao R, Wang Y, Wang W, Zhao D, Niu Y, et al. ANGPTL4 inhibits granulosa cell proliferation in polycystic ovary syndrome by EGFR/JAK1/STAT3-mediated induction of p21. FASEB J. 2023; 37: e22693.
27. Feng H, Li W, Zhan C, Li X, Ye Q. Analysis of factors influencing ovarian reserve in patients with endometriosis. Arch Gynecol Obstet. 2025; 312: 1205-13.

Ovotesticular disorder of sex development presenting in adolescence with amenorrhea and clitoromegaly-what is your diagnosis?

An adolescent girl, aged 12 years presented to the gynecology out-patient department, with concerns of absent breast development and lack of menstruation. Her parents reported a gradual deepening of the voice and progressive enlargement of the clitoris over the past two years. There was no history of cyclic abdominal pain, galactorrhoea, visual disturbances, or chronic illness. There was no history of exogenous androgen exposure or anabolic steroid use. The patient's medical history was unremarkable. There was no history of neonatal ambiguity, salt-wasting crises, or similar conditions in family members. On general examination, the patient appeared tall and thin with an arm span exceeding height. She had poorly developed breasts (Tanner stage I) and minimal axillary and pubic hair (Tanner stage I) (Figure 1). No facial acne or hirsutism was noted. The external genitalia were of female phenotype. On local examination, the vaginal opening was not appreciable, and the uterus was not palpable, clinically. The urinary meatus was normal in position. The clitoris measured 2.5 cm in length and 1.3 cm in width, consistent with clitoromegaly (Figure 2). No dysmorphic features such as webbed neck, shield chest, or low hairline were evident. Systemic examination was otherwise normal. Baseline investigations, including complete blood count, liver, renal, and thyroid function tests, were within normal limits. Endocrine evaluation revealed elevated total serum testosterone of 468 ng/dL (normal: 15-70 ng/dL), low estradiol of 10 pg/mL (normal: 30-400 pg/mL), and reduced anti-Müllerian hormone of 0.60 ng/mL (normal: 1.0-10 ng/mL), suggesting impaired ovarian function and androgen excess. Gonadotropins were elevated, with luteinizing hormone (LH) 13.87 IU/L (normal: 1.9-12.5 IU/L) and follicle-stimulating hormone (FSH) 37.57 IU/L (normal: 2.5-10.2 IU/L), consistent with hypergonadotropic hypogonadism. Dehydroepiandrosterone (DHEA) was within normal limits at 5.60 μg/dL (normal: 1.7-7.0 μg/dL), and 17-hydroxyprogesterone (17-OHP) was low at 0.10 ng/mL (normal: 0.2-1.0 ng/mL), effectively excluding congenital adrenal hyperplasia (CAH). Peripheral blood karyotype demonstrated a 46,XY chromosomal pattern, supporting the diagnosis of ovotesticular disorder with gonadal dysgenesis. Pelvic ultrasonography showed a small uterus with poorly visualized gonads. Magnetic resonance imaging (MRI) of the pelvis demonstrated a left ovary measuring 1.9×1.1 cm along with a uterine remnant, while the right ovary was not visualized. Two testicular structures were identified, with the right located in the perivesical region measuring 1.0×1.2 cm and the left in the inguinal canal measuring 0.5×1.6 cm (Figure 3). Clitoromegaly with underlying cavernous tissue was noted, whereas the remainder of the pelvic organs appeared normal.

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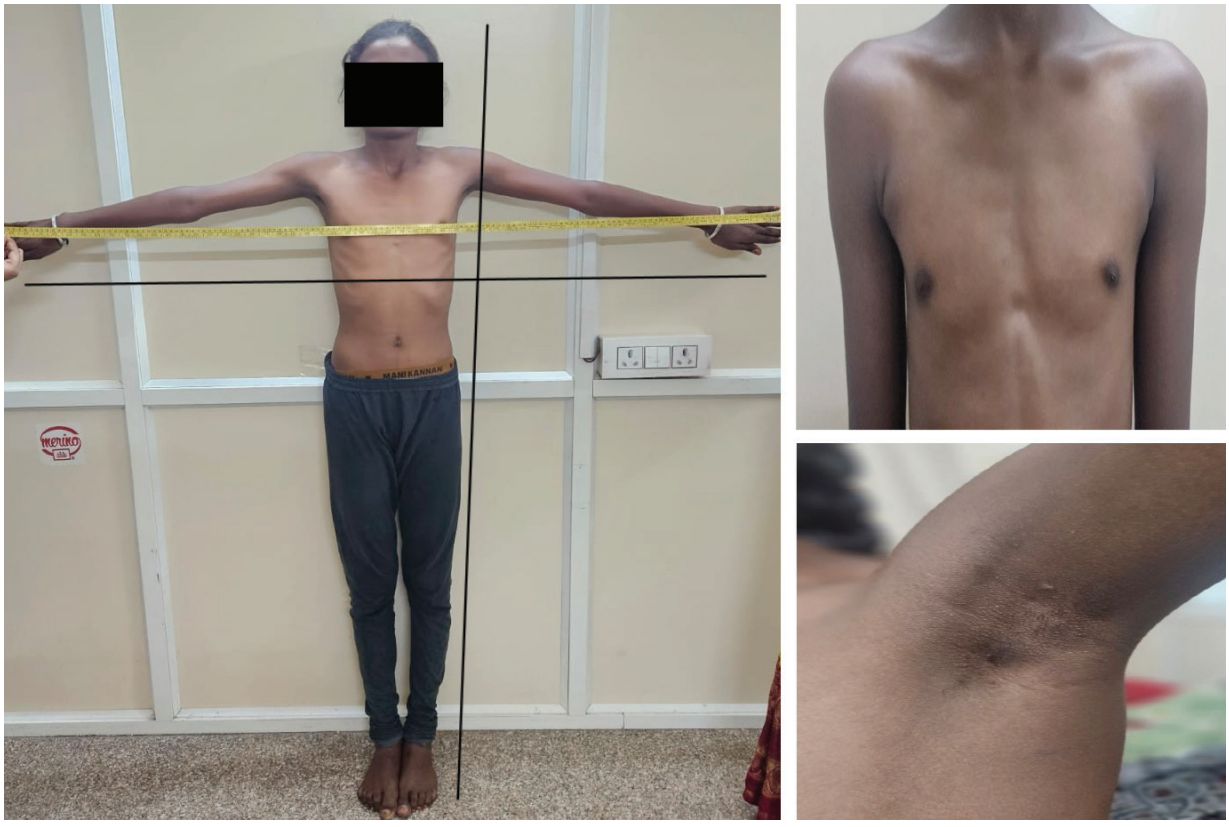

Figure 1. Clinical photograph showing delayed secondary sexual characteristics. The image demonstrates poorly developed breasts, minimal axillary hair, and an arm span greater than height

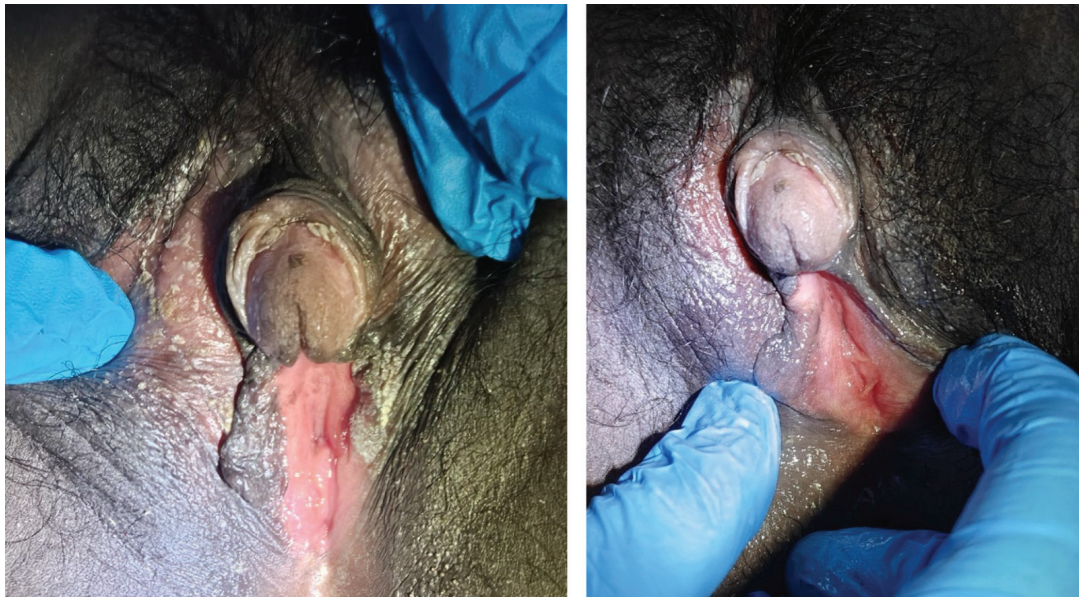

Figure 2. Clinical photograph illustrating clitoromegaly. The image shows enlargement of the clitoral body and glans beyond normal anatomical limits, consistent with clitoromegaly. Note the preservation of labia minora and majora morphology

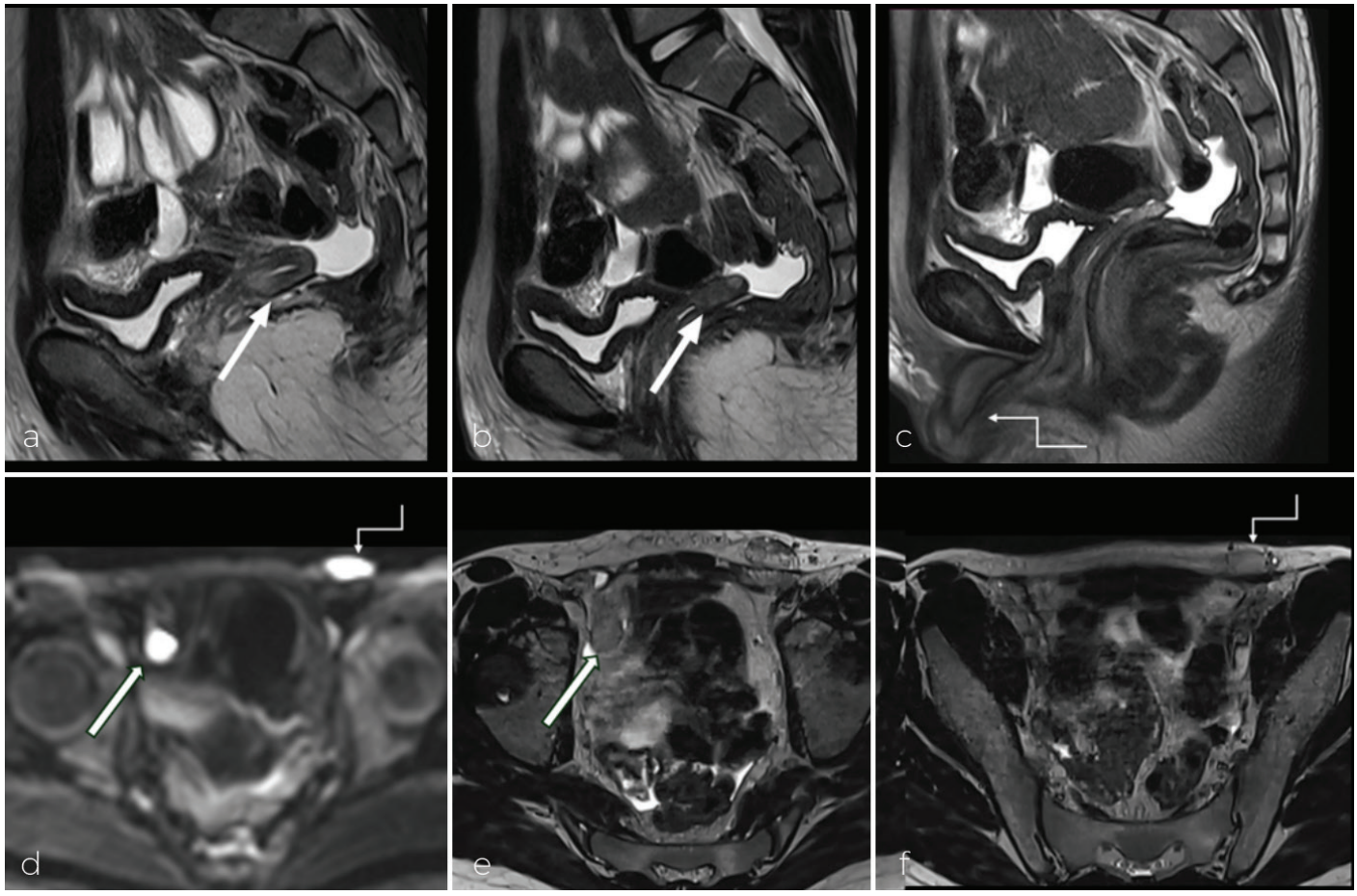

Figure 3. Axial (a) diffusion-weighted imaging and T2 space sequence (b, c) shows T2 homogeneously hyperintense gonads with diffusion restriction in the right side of the pelvis (arrow) and left inguinal region (bent arrow) with no follicles. Sagittal T2 images show a hypoplastic retroverted uterus (arrow in d, e) measuring app. 4 cm x 2.7 cm x 1.3 cm, showing endomyometrial differentiation. Sagittal T2 image (f) shows an enlarged clitoris (bent arrow)

Answer

The diagnosis of 46,XY ovotesticular disorders of sex development (DSD) was made based on a combination of clinical, hormonal, and cytogenetic findings. The patient presented with virilization (clitoromegaly, hoarse voice), delayed puberty, and absent secondary sexual characteristics. Hormonal evaluation showed elevated testosterone with low estradiol and hypergonadotropic hypogonadism. Cytogenetic analysis confirmed a 46,XY karyotype, and imaging suggested the presence of both ovarian and testicular tissue, consistent with ovotesticular DSD with gonadal dysgenesis. The patient was managed with a multidisciplinary approach involving endocrinology, gynecology, and psychiatry. Given her age and ongoing pubertal development, hormone replacement therapy (estrogen) was initiated to induce secondary sexual characteristics, promote bone mineralization, and support psychosocial development. Psychosocial support and genetic counselling were provided, and long-term follow-up was planned to monitor pubertal progression and optimize reproductive health. Definitive gonadal evaluation via laparoscopy and biopsy is planned at 18 years to confirm the presence of ovotesticular tissue and assess malignancy risk, allowing for individualized surgical management. Bone health was supported with calcium and vitamin D supplementation and monitored via DEXA scans. Genital reconstruction (clitoroplasty ± vaginoplasty) is planned after pubertal induction and in consultation with the patient. The patient and family were counselled regarding the nature of the disorder, potential fertility implications, and the importance of long-term follow-up, including monitoring for gonadal tumors and optimizing hormonal therapy. The patient was enrolled in regular follow-up for monitoring of pubertal development and psychological well-being.

46,XY ovotesticular DSD, is among the rarest forms of sexual developmental disorders (1-3). Unlike the more common 46,XX ovotesticular DSD, which often results from *SRY*

translocation, the 46,XY form usually reflects partial testicular dysgenesis or mutations affecting testis-determining genes, such as *SOX9*, *WT1*, or *SF1* (4). The coexistence of ovarian and testicular tissue in the same individual represents incomplete differentiation of bipotential gonads (5). In 46,XY individuals, defective expression of testis-determining genes leads to partial or asymmetric gonadal differentiation, producing an ovotestis on one side and a dysgenetic gonad on the other. The resulting endocrine imbalance causes ambiguous genitalia or, as in this case, delayed puberty and virilization. Residual Leydig cells produce androgens, explaining the hoarse voice and clitoromegaly, while insufficient estrogen production results in absent breast development and delayed skeletal maturation (6). In the present case, reduced AMH indicated impaired Sertoli cell function. Normal DHEA and low 17-OHP excluded CAH.

The patient demonstrated hypergonadotropic hypogonadism, with high LH/FSH and low estradiol, indicating gonadal failure. Testosterone was elevated but insufficient for full virilization, explaining the coexistence of partial androgen effects (clitoromegaly, hoarse voice) and hypogonadal features (poor breast development, sparse axillary hair, increased arm span). MRI showed discordant gonadal anatomy: a left ovary with a uterine remnant, an absent right ovary, and bilateral dysgenetic testes. The risk of gonadal malignancy is higher in patients with Y chromosome material, underscoring the need for biopsy or gonadectomy. Molecular studies (*SRY*, *SOX9*, *NR5A1*, *WT1*, *DMRT1*) are recommended to clarify the etiology.

Patients with 46,XY ovotesticular DSD are at increased risk of gonadal malignancy, particularly gonadoblastoma and dysgerminoma, due to the presence of Y chromosome material and dysgenetic gonads (7). Therefore, prophylactic gonadectomy is generally recommended on the side of dysgenetic or testicular tissue. However, in this patient histopathological evaluation was deferred until late adolescence. This approach is clinically acceptable, as early invasive procedures can interfere with natural pubertal development, especially if hormone replacement therapy is initiated to induce secondary sexual characteristics. Planned laparoscopy and targeted biopsy at 18 years allow for a more mature and accurate assessment of gonadal tissue, aiding individualized surgical planning, including malignancy risk stratification and potential fertility preservation. Close clinical monitoring, imaging, and hormonal follow-up in the interim ensure patient safety, consistent with current recommendations from the Chicago Consensus and ESPE guidelines for DSD management (8).

Malignancy risk in dysgenetic gonads is heterogeneous and depends on the specific DSD diagnosis, presence of Y-chromosome material, and degree of gonadal dysgenesis. Individuals with Y-bearing dysgenetic gonads are at substantially increased risk for gonadoblastoma and other germ cell tumors compared with 46,XX ovotesticular DSD, but reported risk estimates vary between studies. Contemporary reviews place the overall tumor risk in dysgenetic gonads broadly from low single-digit percentages in some ovotesticular series to much higher rates reported in cohorts of 46,XY gonadal dysgenesis or mixed gonadal dysgenesis (range quoted across series ~3% up to 25% or more), reflecting heterogeneity of case mix and diagnostic criteria (9,10). Guidance from multidisciplinary DSD consensus documents and contemporary cohort studies supports individualized timing of gonadectomy. For high-risk diagnoses with frank dysgenetic testicular tissue and Y-material (for example, classic 46,XY complete gonadal dysgenesis), early prophylactic gonadectomy is generally recommended because of the higher malignancy risk. For conditions with lower and more uncertain risk, such as some ovotesticular presentations, delaying gonadectomy until late adolescence (commonly around age 16–18 years) may be reasonable if there is careful clinical and imaging surveillance, because delay permits pubertal induction, assessment of pubertal progression, and time for shared decision-making about gender, fertility preservation and psychosocial support. This approach is supported by cohort data and expert consensus placing the optimal timing for prophylactic gonadectomy in many Y-bearing phenotypic females at around 16–18 years, with earlier surgery when imaging or clinical features are suspicious.

Psychosocial counselling forms a cornerstone of management, addressing gender identity, fertility expectations, and body image. Hormonal therapy should be individualized, balancing feminizing and metabolic needs while ensuring adequate bone mineralization. Table 1 presents the close differential diagnoses, highlighting conditions with overlapping clinical, hormonal, and imaging features that should be considered to guide accurate evaluation and management. With timely diagnosis and appropriate management, patients can achieve satisfactory secondary sexual development and psychosocial adjustment. Lifelong follow-up is essential to monitor for neoplastic transformation, bone health, and hormonal balance (11,12).

46,XY ovotesticular DSD with gonadal dysgenesis is an exceedingly rare but clinically significant cause of delayed puberty and virilization in phenotypic females. A combination of detailed clinical evaluation, hormonal profiling, imaging, and histopathological confirmation is essential for accurate diagnosis. Early gonadectomy of dysgenetic tissue, hormone replacement therapy, and psychological support form the cornerstone of management. Early recognition and multidisciplinary management are crucial for guiding gender assignment, monitoring malignancy risk, and ensuring psychosocial support.

Table 1. Close differentials of 46,XY ovotesticular DSD (2,5,8,11)

Disorder	Karyotype	Gonads	Internal structures	External genitalia	Hormone profile	Key differentiating features
Ovotesticular DSD	46,XY (rare)	Ovotestis ± ovary/testis	Uterine remnant ± Wolffian derivatives	Ambiguous; clitoromegaly/ undervirilized male	Variable T/E_2; ↑LH/FSH	Both ovarian and testicular tissue (histology)
Mixed gonadal dysgenesis	45,X/46,XY mosaic	Dysgenetic testis + streak gonad	Often a hemi-uterus, Müllerian remnants	Ambiguous, asymmetric	↑FSH/LH, low sex steroids	Asymmetric gonads; mosaicism
46,XY complete gonadal dysgenesis (Swyer)	46,XY	Bilateral streak gonads	Normal uterus and tubes	Normal female	Very low T/E_2; ↑↑FSH/LH	No testicular tissue; pure streak gonads
Partial androgen insensitivity syndrome	46,XY	Testes (inguinal/ abdominal)	Absent uterus (AMH active)	Under virilized male/ambiguous	High T; normal/↑LH	Testes only, uterus absent

DSD: Disorders of sex development, LH: Luteinizing hormone, FSH: Follicle-stimulating hormone, AMH: Anti-Müllerian hormone

Ethics

Informed Consent: *Written informed consent for publication, including images and clinical details, was obtained from the patient and her legal guardians.*

Footnotes

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

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References

1. Acién P, Acién M. Disorders of sex development: classification, review, and impact on fertility. J Clin Med. 2020; 9: 3555.
2. De Jesus Escano MR, Mejia Sang ME, Reyes-Mugica M, Colaco M, Fox J. Ovotesticular disorder of sex development: approach and management of an index case in the Dominican Republic. Cureus. 2021; 13: e18512.
3. Krstić ZD, Smoljanić Z, Vukanić D, Varinac D, Janjić G. True hermaphroditism: 10 years' experience. Pediatr Surg Int. 2000; 16: 580-3.
4. Scarpa MG, Grazia MD, Tornese G. 46,XY ovotesticular disorders of sex development: a therapeutic challenge. Pediatr Rep. 2017; 9: 7085.
5. Makiyan Z. Studies of gonadal sex differentiation. Organogenesis. 2016; 12: 42-51.
6. Chavez TF, Singh M, Avadhani V, Leonis R. Leydig tumor in normal sized ovaries causing clitoromegaly: a case report. Gynecol Oncol Rep. 2024; 52: 101345.
7. Griggers JI, Higgins R, Terris MK. Ovarian malignancy in an individual with 46,XY ovotesticular disorder of sexual development - a case report. Urol Case Rep. 2024; 53: 102680.
8. Hughes IA, Houk C, Ahmed SF, Lee PA; LWPES Consensus Group; ESPE Consensus Group. Consensus statement on management of intersex disorders. Arch Dis Child. 2006; 91: 554-63.
9. Kilberg MJ, McLoughlin M, Pyle LC, Vogiatzi MG. Endocrine management of ovotesticular DSD, an index case and review of the literature. Pediatr Endocrinol Rev. 2019; 17: 110-6.
10. Morin J, Peard L, Saltzman AF. Gonadal malignancy in patients with differences of sex development. Transl Androl Urol. 2020; 9: 2408-15.
11. Verkauskas G, Jaubert F, Lortat-Jacob S, Malan V, Thibaud E, Nihoul-Fékété C. The long-term followup of 33 cases of true hermaphroditism: a 40-year experience with conservative gonadal surgery. J Urol. 2007; 177: 726-31; discussion 731.
12. Sircili MH, Denes FT, Costa EM, Machado MG, Inacio M, Silva RB, et al. Long-term followup of a large cohort of patients with ovotesticular disorder of sex development. J Urol. 2014; 191 :1532-6.

Suspected burned-out ovarian germ cell tumor in Turner mosaicism: a diagnostic challenge-what is your diagnosis?

A 31-year-old nulliparous woman presented to the gynecology outpatient department with primary amenorrhea and intermittent lower abdominal pain of 10-15 days' duration. She reported a single episode of scant vaginal spotting eight years earlier. There was no history of cyclical abdominal pain, hormonal therapy, or prior evaluation for primary amenorrhea.

On general examination, she was conscious and oriented, of short stature (height 135 cm), and thinly built with a body mass index of 18.02 kg/m^2. Head and neck examination revealed a diffusely enlarged thyroid gland with multiple palpable nodules, without compressive symptoms. Cardiovascular and respiratory examinations were within normal limits.

Secondary sexual characteristics were poorly developed, with Tanner stage II breast development, absent axillary hair, and sparse pubic hair (Figure 1). Abdominal examination revealed a firm, tender abdominopelvic mass corresponding to a 26-28-week gravid uterus, predominantly cystic in consistency. External genital examination showed hypoplastic labia majora and minora, with a normal-appearing vagina.

Laboratory investigations revealed markedly elevated thyroid-stimulating hormone levels (70.8 μIU/mL) with strongly positive anti-thyroid peroxidase antibodies (>1100 IU/mL), consistent with autoimmune thyroiditis. Gonadotropins were significantly increased (follicle-stimulating hormone 127.99 mIU/mL, luteinizing hormone 47.23 mIU/mL) with low estradiol levels (17.5 pg/mL), indicating a hypergonadotropic hypogonadal state. Lactate dehydrogenase (LDH) was elevated (364 U/L), and cancer antigen-125 (CA125) was mildly raised (42.4 U/mL), while alpha-fetoprotein (2.88 ng/mL) and β-human chorionic gonadotropin (3.40 mIU/mL) were within normal limits. All other investigations, including complete blood counts, liver and renal function tests, coagulation profile, and chest radiography, were unremarkable.

Neck ultrasonography showed altered echotexture of both thyroid lobes with a multinodular goiter in the right lobe. Pelvic ultrasonography revealed a large, well-defined multiloculated cystic lesion arising from the right adnexa, with multiple internal septations. One septum measured 4-4.5 mm and showed mild vascularity. Papillary excrescences measuring 2×0.5 cm were noted inferiorly without vascularity. Internal echoes were present, with no mural nodules or calcifications (Figure 2). The right ovary was not visualized separately. The uterus was small (3.9×1.8×3.2 cm) with an ill-defined endomyometrial junction, and the left ovary was not seen.

Magnetic resonance imaging confirmed a hypoplastic uterus measuring approximately 3×6 cm, with a uterus-to-cervix ratio of 2:1 and an endometrial thickness of 2 mm. A large, thin-walled, multiloculated cystic lesion (10.6×7.2×10.2 cm) extended from the midline pelvis to the lower abdomen, reaching the level of the umbilicus. The lesion was T1 hypointense and T2 hyperintense, with irregular thickened septations (maximum thickness 5.4 mm). Some locules showed T1/FS hyperintensity, suggestive of hemorrhagic or proteinaceous content. Neither of the ovaries was visualized separately. Minimal perilesional omental edema was present, without significant lymphadenopathy or ascites. A heterogeneously enhancing tissue, extending from the uterus to the cystic lesion

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was noted, likely representing an edematous pedicle. Overall imaging features raised concern for a high-risk adnexal lesion in the setting of uterine hypoplasia (Figure 3).

Given the clinical suspicion of Turner syndrome (TS) or mosaic TS, cytogenetic evaluation was performed. Karyotyping and chromosomal microarray analysis demonstrated a 56.7-Mb deletion involving Xp22.33-Xp11.1, consistent with a structural X chromosome abnormality (Xp deletion syndrome) presenting with TS-like features, rather than classical 45,X TS (Figure 4).

Figure 1. Standing clinical photograph demonstrating short stature, underdeveloped secondary sexual characteristics, and diffuse neck enlargement

On the third day of admission, the patient developed sudden, severe abdominal pain associated with vomiting, tachycardia, and altered sensorium. In view of suspected adnexal torsion, she underwent emergency staging laparotomy under general anesthesia, despite being high-risk due to markedly elevated TSH levels. Preoperative imaging had demonstrated a large complex adnexal mass with thickened septations and papillary excrescences, accompanied by elevated LDH and mildly raised CA125 levels, raising concern for an underlying ovarian malignancy or germ cell tumor. Given the diagnostic uncertainty and the increased risk of germ cell tumors in patients with an Xp deletion syndrome and Turner phenotype, comprehensive surgical staging was performed to ensure appropriate oncologic management and avoid the need for a second procedure.

Answer

Surgery revealed a large right adnexal cystic mass measuring approximately 12×10×11 cm, with omentum adherent to its superior surface. The pedicle showed three complete twists, one of which appeared chronic with dense adhesions and was not amenable to detorsion. The uterus was hypoplastic, the left ovary was a streak gonad, and the right adnexa was incorporated into the mass (Figure 5). Minimal blood-tinged fluid was present in the pouch of Douglas and was sent for cytology. After partial detorsion, a right salpingo-oophorectomy was performed, followed by total abdominal hysterectomy, left salpingo-oophorectomy, bilateral pelvic lymph node dissection, and omental and peritoneal biopsies.

Gross examination showed a cystic right adnexal mass measuring 12.5×11.5 cm with a congested external surface and intact capsule. The cut surface was multiloculated, containing approximately 100 mL of hemorrhagic fluid, with no identifiable viable areas. The uterus and cervix were hypoplastic (6×3.5×1 cm). The left ovary was a streak gonad measuring 0.8×0.8 cm.

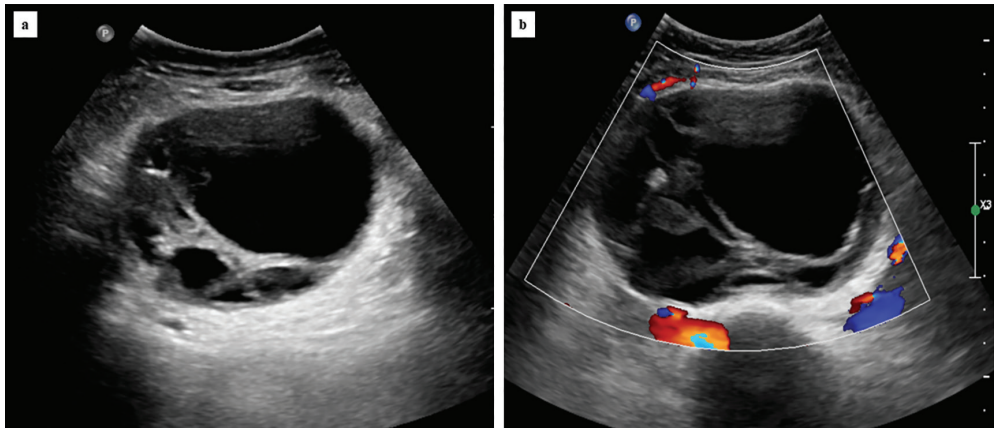

Figure 2. (a) Axial ultrasound image-large thick-walled multiloculated cystic lesion with thick internal separations; (b) On colour Doppler, minimal uptake is noted only in the wall of the lesion

Microscopically, the right adnexal specimen, including the cyst wall and residual streak gonadal tissue, was extensively sampled (20 tissue blocks). Sections revealed a fibrocollagenous cyst wall with extensive hemorrhagic necrosis and granulation tissue formation, without viable epithelial lining or identifiable ovarian parenchyma. The left streak gonad was entirely submitted for histopathological examination (2 tissue blocks) and consisted of fibrocollagenous and adipose tissue, with no follicles or ovarian stroma. Both fallopian tubes showed vascular congestion with poorly developed plicae. The endometrium was thin and inactive, lacking cyclical changes. Pelvic lymph nodes, omental and peritoneal biopsies were unremarkable, and peritoneal fluid cytology was negative for malignancy. Owing to extensive hemorrhagic ischemic necrosis with complete loss of viable tissue, the exact nature of the adnexal cyst could not be definitively established (Figure 6). Immunohistochemical studies were not performed, as the absence of viable tumor cells rendered them non-contributory. TS results from the complete or partial loss of one sex chromosome and affects approximately 1 in 2,500-3,000 live female births. Its clinical spectrum is broad, encompassing short stature, ovarian dysfunction, and variable neurocognitive features (1,2). Cytogenetically, TS is heterogeneous and only about 40% of individuals exhibit a classic 45, X karyotype, while

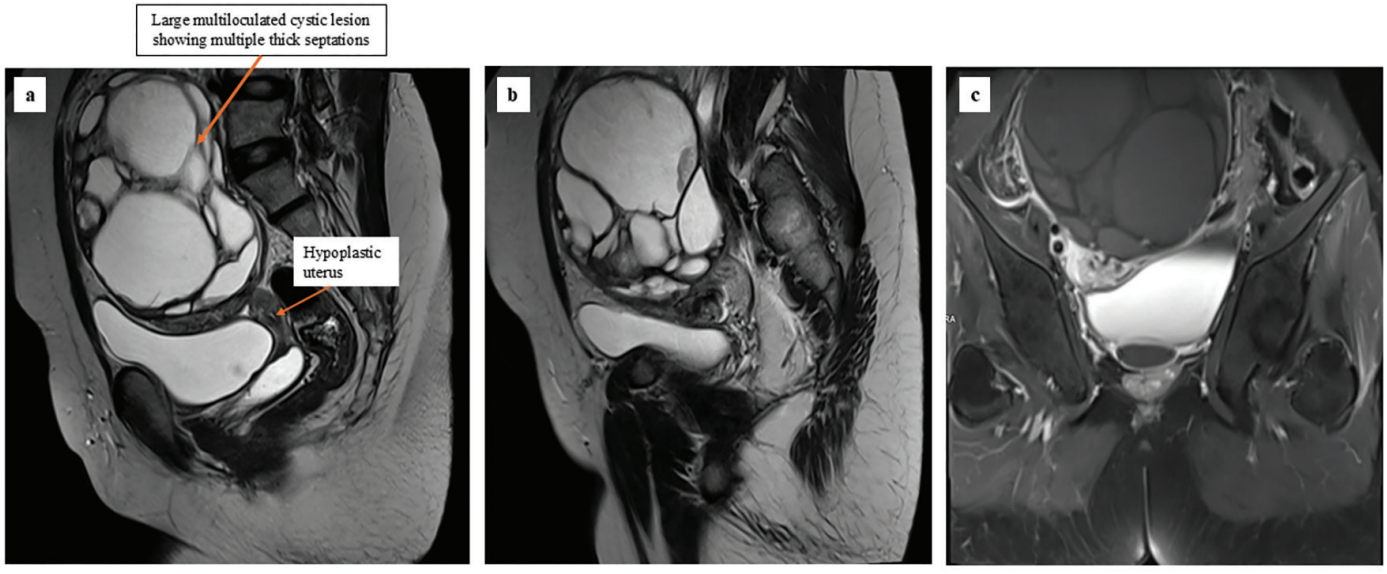

Figure 3. (a) Sagittal T2W image shows a hypoplastic uterus with preserved zonal anatomy. The right adnexal thick-walled multiloculated lesion is noted abutting the fundus and indenting the dome of the urinary bladder; (b) Right parasagittal T2W image shows edematous, thickened pedicle of the ovarian lesion; (c) Post-contrast T1FS coronal image. A thickened pedicle is seen. The ovarian lesion shows smooth wall enhancement. There is no enhancement of septations

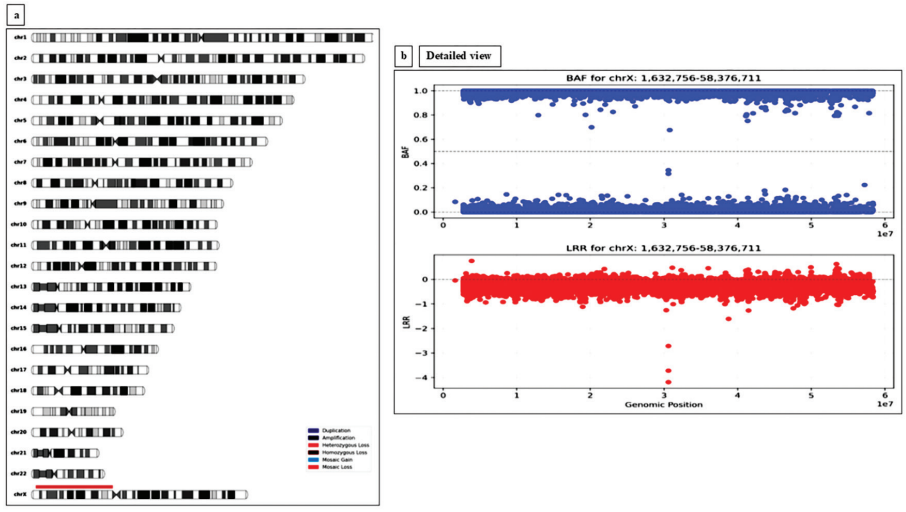

Figure 4. (a) Karyoview; (b) Detailed view of Xp22.33p11.1

the remainder show mosaicism or structural abnormalities such as deletions, ring chromosomes, or isochromosomes (2). Normal ovarian development and fertility depend on the structural and functional integrity of the X chromosome. In TS, accelerated germ cell apoptosis begins early in fetal life, leading to depletion of the primordial follicle pool, impaired folliculogenesis, and streak gonad formation (3). This process has been attributed to abnormal meiotic pairing of the X chromosome, disrupted oocyte–granulosa cell interactions, and haploinsufficiency of key X-linked genes involved in ovarian maintenance, including *BMP15* and *PGRMC1* (3,4). Clinically, most individuals develop primary ovarian insufficiency, diagnosed by amenorrhea with elevated gonadotropins reflecting hypergonadotropic hypogonadism, although a subset demonstrates partial pubertal development, menarche, or even spontaneous fertility (3).

Diagnosis of TS relies primarily on conventional karyotyping, typically assessing 15-30 metaphases, with expanded analysis recommended when mosaicism is suspected (2,3). However, standard karyotype and chromosomal microarray techniques may fail to detect low-level or tissue-restricted Y-chromosome mosaicism, referred to as "hidden Y mosaicism," for which molecular methods and fluorescence *in situ* hybridization (FISH) may be required (5,6). In the present case, additional molecular testing, including FISH or polymerase chain reaction-based analysis for Y-chromosome sequences, could not be performed because of financial constraints. Consequently, the presence of occult low-level or tissue-restricted Y-chromosome mosaicism cannot be completely excluded.

Furthermore, the reported prevalence of Y-chromosome material in TS varies widely (4-61%), depending on the detection method, and carries a clinically significant risk of 10-30% for gonadoblastoma (7).

Individuals with TS and dysgenetic gonads are therefore at increased risk for gonadal germ cell tumors. Gonadal dysgenesis reflects abnormal fetal gonadal development resulting from sex chromosome abnormalities or mutations in genes that regulate urogenital ridge formation and sex determination (8). Among germ cell tumors associated with dysgenetic gonads, gonadoblastoma is the most characteristic lesion. It is a borderline neoplasm composed of germ cell and sex cord elements, frequently bilateral, and capable of malignant transformation, most commonly into dysgerminoma or seminoma, in up to one-third of cases (7,9). Dysgerminoma, the ovarian counterpart of testicular seminoma, typically presents in adolescents and young women and is often associated with elevated serum LDH levels, which may aid in diagnosis and follow-up (10-12). Moreover, the mildly

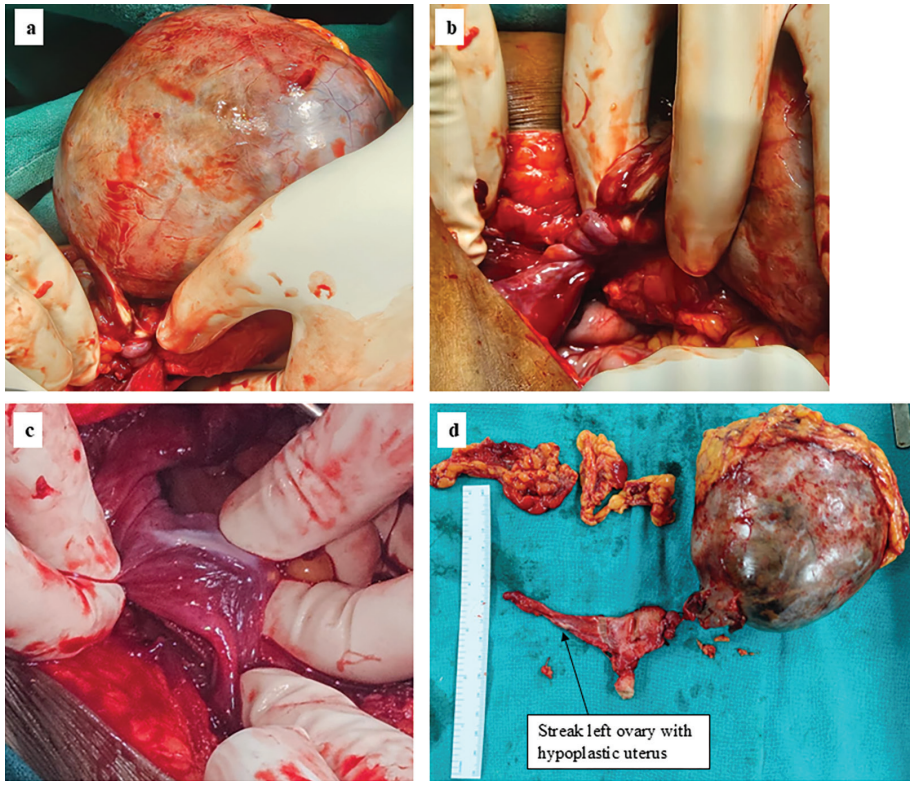

Figure 5. (a, b) Intraoperative images showing a large right adnexal mass with multiple twists in the pedicle; (c) Left streak ovary with fibrous appearance; (d) Post-hysterectomy specimen showing a hypoplastic uterus with a streak left ovary and a large right adnexal cyst with lymph nodes and omental biopsy

elevated serum CA125 level observed in the present case may be attributable to chronic adnexal torsion, inflammation, and extensive hemorrhagic necrosis rather than malignancy alone, as has been reported in previous studies (13).

In the present case, Y-chromosome material was not identified on chromosomal microarray analysis. Nevertheless, given the dysgenetic gonadal phenotype and tumor characteristics, the possibility of occult or low-level Y mosaicism cannot be definitively excluded. An additional diagnostic consideration is the phenomenon of spontaneous tumor regression. "Burned-out" germ cell tumors are well documented in the testis, particularly in seminoma and embryonal carcinoma, where the primary lesion undergoes regression, leaving fibrotic or necrotic remnants, sometimes in the presence of metastatic disease (14,15). In contrast, spontaneous regression of ovarian germ cell tumors is exceedingly rare, and true burned-out ovarian dysgerminoma remains poorly characterized (16).

In this patient, chronic adnexal torsion resulted in extensive hemorrhagic necrosis with complete loss of viable tumor tissue, accompanied by elevated serum LDH levels and bilateral dysgenetic gonads in the setting of Xp deletion syndrome with a Turner phenotype. While ischemic necrosis from long-standing torsion is a plausible explanation, the overall clinicoradiological and biochemical profile raises the possibility of a burned-out ovarian germ cell tumor. Although definitive confirmation is limited by the absence of residual or metastatic disease, this presentation broadens the differential diagnosis of adnexal masses in patients with a TS phenotype.

This case also has important implications for endocrinologists, pediatricians, gynecologists, and pathologists involved in the care of individuals with TS and disorders of sex development. Patients with features of TS presenting with primary amenorrhea, hypergonadotropic hypogonadism, dysgenetic gonads, or adnexal masses should undergo comprehensive genetic evaluation, including assessment for occult Y-chromosomal material when clinically indicated, as its presence significantly increases the risk of gonadoblastoma and other germ cell tumors. Although no Y-chromosome material was detected in the present case, the possibility of low-level or tissue-restricted mosaicism cannot be completely excluded. This highlights the importance of individualized risk stratification, timely consideration of prophylactic gonadectomy in high-

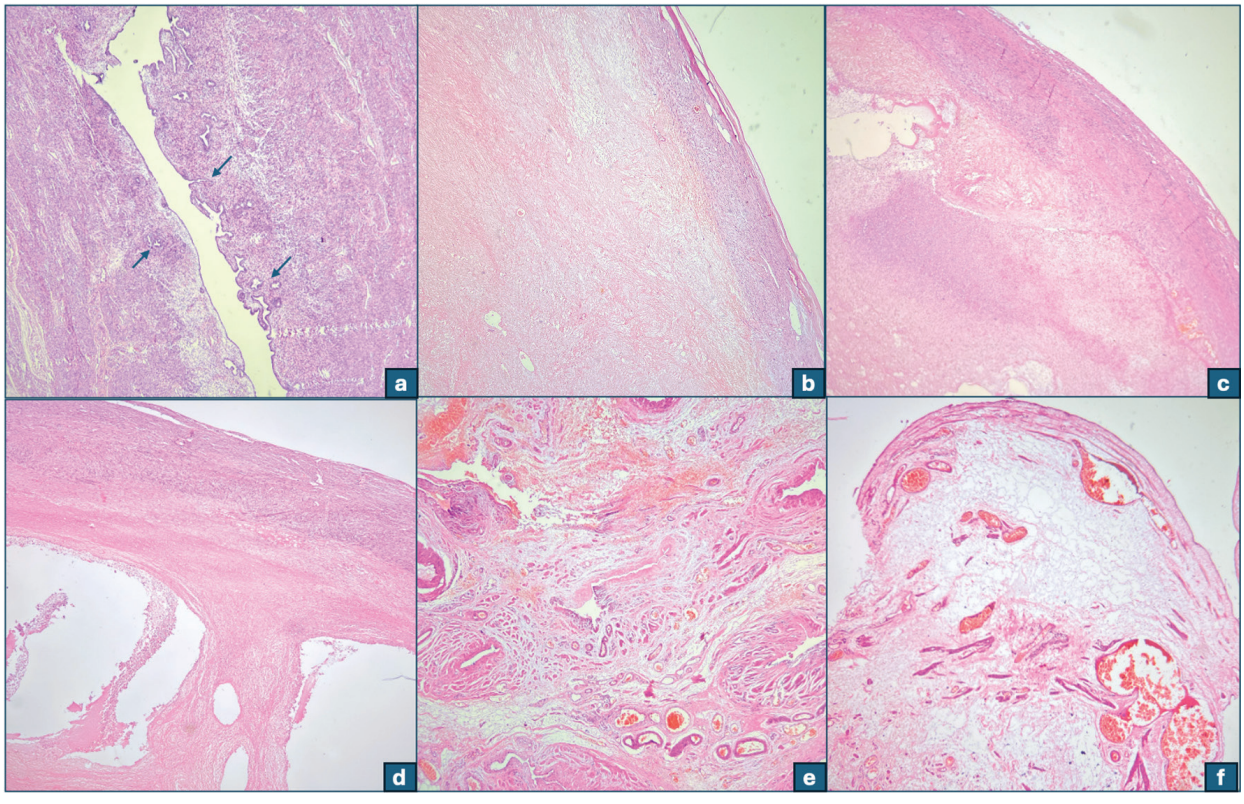

Figure 6. (a) Hypoplastic uterus showing poorly developed endometrial lining (arrow) with scant, inactive glands (H&E, 40x); (b-d) Right adnexal cyst demonstrating extensive haemorrhagic necrosis with loss of viable epithelial lining, precluding definitive characterization of the cyst [(H&E, 40x (b),100x (c)]; (e, f) Left and right streak gonads composed predominantly of fibrocollagenous stroma with variably sized blood vessels with complete absence of ovarian follicles or parenchyma (H&E, 100x)

H&E: Hematoxylin and eosin

risk patients, and multidisciplinary management involving gynecology, endocrinology, pathology, genetics, and pediatric specialists to optimize diagnosis, surgical decision-making, long-term endocrine care, and surveillance.

This case illustrates the diagnostic complexity of evaluating ovarian and adnexal masses in patients with Xp deletion syndrome presenting with a Turner phenotype and gonadal dysgenesis. Even in the absence of detectable Y-chromosome material on standard testing, low-level or tissue-restricted mosaicism cannot be excluded. The coexistence of a large adnexal mass, elevated LDH, and extensive hemorrhagic necrosis without viable tumor tissue raises suspicion of a burned-out ovarian germ cell tumor, an entity well recognized in the testis but rarely described in the ovary. This report expands the limited literature on atypical presentations of germ cell tumors in patients with Xp deletion syndrome and a Turner phenotype. Furthermore, this case highlights the need for heightened clinical vigilance, thorough clinicopathologic correlation, individualized surgical management, and long-term surveillance in patients with dysgenetic gonads.

Ethics

Informed Consent: *Written informed consent was obtained from the patient both for participation in the study and for publication of the relevant data.*

Footnotes

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

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References

1. Ibarra-Ramírez M, Campos-Acevedo LD, Martínez de Villarreal LE. Chromosomal abnormalities of interest in Turner syndrome: an update. J Pediatr Genet. 2023; 12: 263-72.
2. Madison A, Applegate C, Stinnett V, Miranda DM, Cross C, Vaught KC, et al. Cytogenomic characterization of mosaic X-ring chromosomes in seventeen patients with Turner syndrome (TS)-42 years of experience at a single-site institution. Sci Rep. 2025; 15: 12836.
3. Porcu E, Cipriani L, Damiano G. Reproductive health in Turner's syndrome: from puberty to pregnancy. Front Endocrinol (Lausanne). 2023; 14: 1269009.
4. Fukami M. Ovarian dysfunction in women with Turner syndrome. Front Endocrinol (Lausanne). 2023; 14: 1160258.
5. Bispo AV, Burégio-Frota P, Oliveira dos Santos L, Leal GF, Duarte AR, Araújo J, et al. Y chromosome in Turner syndrome: detection of hidden mosaicism and the report of a rare X;Y translocation case. Reprod Fertil Dev. 2014; 26: 1176-82.
6. Udo EQ, Truly T, Peters A, Prakash SK, Rivera M, Rodriguez-Buritica DF. Hidden Y Chromosome material and congenital cardiovascular malformations in a cohort of Turner syndrome patients with 45,X blood karyotype. Cytogenet Genome Res. 2023; 163: 290-4.
7. Shen W, Li Y. Gonadoblastoma in Turner syndrome with puberty delay: a case report and literature review. Mol Genet Genomic Med. 2023; 11: e2300.
8. Yüce Ö, Döğer E, Çelik N, Emeksiz HC, Çamurdan MO, Bideci A, et al. Gonadoblastoma with dysgerminoma in a phenotypically turner-like girl with 45,X/46,XY karyotype. J Clin Res Pediatr Endocrinol. 2015; 7: 336-9.
9. Raafey MA, Abdulwaasey M, Fatima SS, Uddin Z, Tariq MU. Bilateral gonadoblastoma with dysgerminoma in a phenotypically normal female with 46XX karyotype: report of a rare case and literature review. Cureus. 2020; 12: e8990.
10. Mitranovici MI, Chiorean DM, Mureşan MC, Buicu CF, Moraru R, Moraru L, et al. Diagnosis and management of dysgerminomas with a brief summary of primitive germ cell tumors. Diagnostics (Basel). 2022; 12: 3105.
11. Amante S, Félix A, Cunha TM. Ovarian dysgerminoma: clues to the radiological diagnosis. Diagn Interv Radiol. 2023; 29: 18-23.
12. Chandrapattan P, Jena A, Patnayak R, Mangaraj S, Naik S, Panda S. Gonadoblastoma with dysgerminoma presenting as virilizing disorder in a young child with 46, XX karyotype: a case report and review of the literature. Case Rep Endocrinol. 2022; 2022: 5666957.
13. Suh DS, Moon SH, Kim SC, Joo JK, Park WY, Kim KH. Significant simultaneous changes in serum CA19-9 and CA125 due to prolonged torsion of mature cystic teratoma of the ovary. World J Surg Oncol. 2014; 12: 353.
14. Sanseverino R, Baio R, Addesso M, Napodano G, Di Mauro U, Intilla O, et al. 'Burned-out' syndrome of testicular teratoma: a case report. Mol Clin Oncol. 2021; 15: 262.
15. Samnani S, Alimohamed N. Case - "Burned-out" testicular tumor: a rare entity with diagnostic dilemma. Can Urol Assoc J. 2022; 16: E572-E4.
16. Kontosis A, Barroeta JE. Gonadoblastoma. PathologyOutlines.com website. https://www.pathologyoutlines.com/topic/ovarytumorgonadoblastoma.html. Accessed December 23rd, 2025.

Accessory cavitated uterine mass: a rare cause of severe dysmenorrhea

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Abstract

We present a rare Müllerian anomaly known as "accessory cavitated uterine mass (ACUM)," which causes severe, refractory dysmenorrhea, and review the literature. A 17-year-old patient experienced severe, cyclic left-sided pelvic pain, correlating with menstruation. Magnetic resonance imaging (MRI) revealed a cystic lesion surrounded by myometrial tissue. Medical treatment with oral contraceptives was unsuccessful. Laparoscopic excision of the mass was performed, and histopathology confirmed the diagnosis of ACUM. At six months postoperatively, she remained asymptomatic, and follow-up MRI showed a normal-appearing uterus. ACUM is a rare Müllerian anomaly that is challenging to diagnose preoperatively, even with advanced imaging. Surgical excision remains the definitive treatment. This case highlights the importance of clinicians considering Müllerian anomalies in adolescents presenting with severe dysmenorrhea. [J Turk Ger Gynecol Assoc. 2026; 27(3): 222-25]

Keywords: Accessory cavitated uterine mass, ACUM, severe dysmenorrhea, Müllerian anomaly, juvenile cystic adenomyosis

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Introduction

Dysmenorrhea affects nearly 80% of adolescents, with severe cases that may indicate rare Müllerian duct anomalies, such as "accessory cavitated uterine mass (ACUM)" (1). ACUM is characterized by progressive worsening of dysmenorrhea, potentially related to gubernaculum dysfunction, and the presence of a non-communicating, accessory uterine cavity, without other uterine anomalies (2-4). Differential diagnoses include juvenile cystic adenomyosis, rudimentary cavitated uterine horns, and degenerated leiomyomas. Diagnostic criteria for ACUM include an isolated accessory cavitated mass; a normal uterus, fallopian tubes, and ovaries; excised mass with confirmatory histopathological examination; an accessory cavity lined by endometrial epithelium with glands and stroma; chocolate-brown fluid content; and no adenomyosis except for small foci of myometrium adjacent to the mass. ACUMs are typically located on the anterior uterine wall (3).

ACUM is an uncommon pathological condition, primarily observed in young individuals, characterized by severe dysmenorrhea and recurrent pelvic pain (5). The accompanying pain often localizes to the side of the mass and does not respond well to non-steroidal anti-inflammatory drugs (NSAIDs) or combined oral contraceptives (COC) (3). The primary treatment for ACUM is surgical excision, which provides permanent relief and recovery. We present a 17-year-old adolescent girl diagnosed with ACUM, detailing her diagnostic process, surgical management, and follow-up visits.

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Case report

A left-sided 27x10 mm mass with a hemorrhagic component on the anterior corpus of the uterus, suggesting a non-communicating uterine horn, was detected by pelvic ultrasound in a 17-year-old patient with severe cyclic dysmenorrhea. Pelvic magnetic resonance imaging (MRI) revealed a hemorrhagic segment within the mass, surrounded by myometrial tissue (Figure 1). Laparoscopic mass excision with diagnostic hysteroscopy was scheduled to assess for any ostia from the cavitated mass into the endometrial cavity, after refractory pain during medical treatment with COC.

Both tubal ostia were patent during hysteroscopy, which revealed a regular endometrial cavity without signs of any accessory cavity or ostia.

Subsequently, laparoscopic resection of the mass was performed (Figures 2-5). A brief video of the operation is available in Video 1. The following steps were performed during surgery. Firstly, the opening of the anterior surface of the uterine peritoneum. After that, a uterine mass was observed on the left side of the uterus. The incision was extended along the left round ligament. Unipolar cautery was used for the excision of the mass. During cauterization, chocolate-brown colored endometriotic fluid was released from the cavitated uterine mass. The fluid was aspirated from the cavitated mass. Following that step, the ACUM was enucleated from the uterus. After the excision of the mass, the resulting uterine defect was repaired with V-Loc™ suture.

The procedure was well tolerated with no postoperative complications. She was discharged the next day. Histopathology confirmed the endometrial glands and stroma within the cavity tissue, with small foci of adenomyosis in the adjacent myometrium. At six months postoperatively, she reported resolution of dysmenorrhea with regular menstrual cycles, and

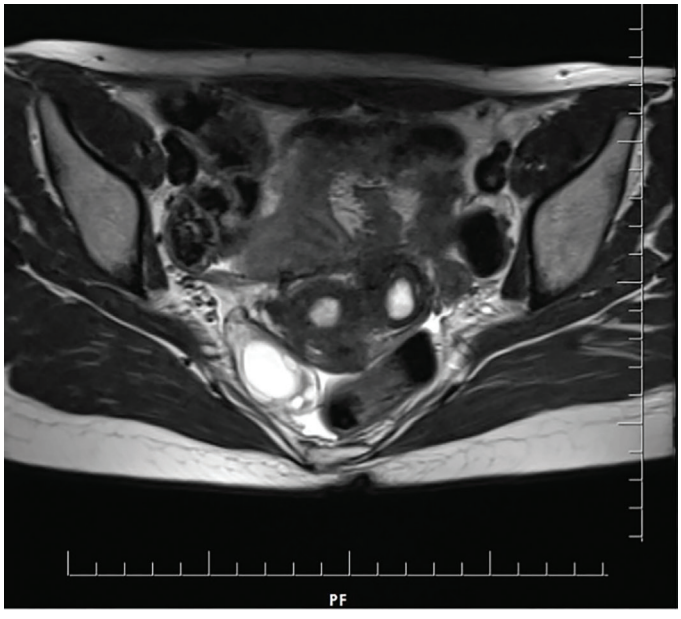

Figure 1. T2-weighted magnetic resonance imaging image of the mass (accessory cavitated uterine mass)

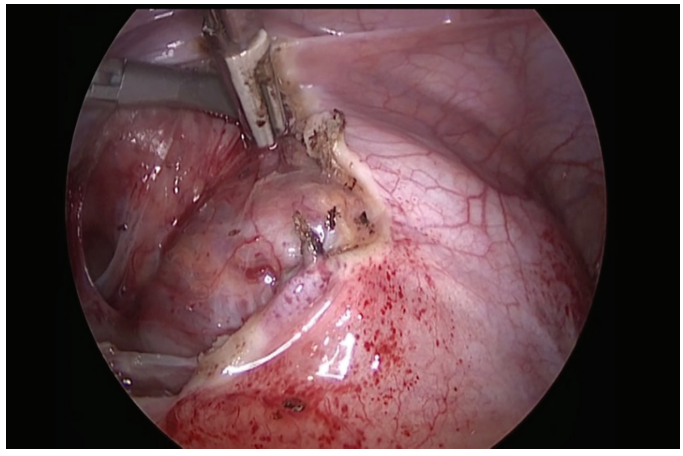

Figure 2. Opening of the anterior surface of the uterine peritoneum

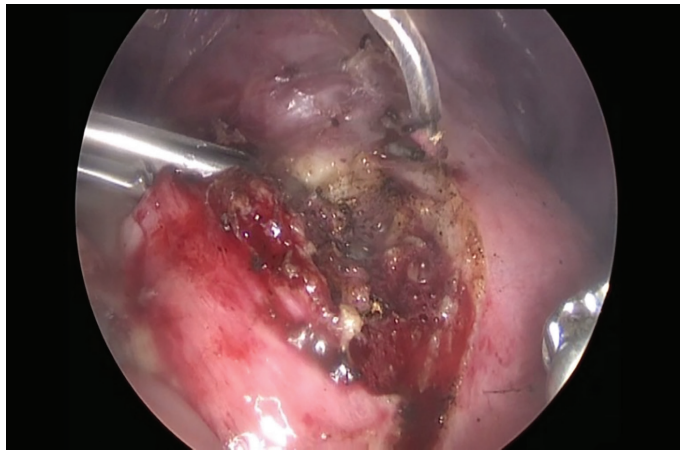

Figure 3. Endometrial lumen of the accessory cavitated uterine mass

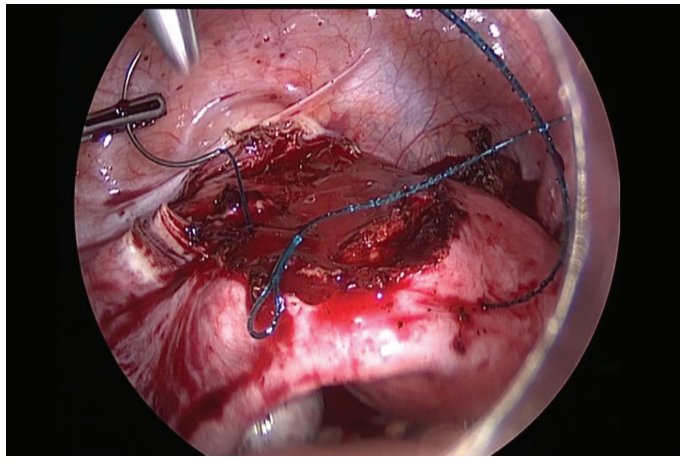

Figure 4. Suturing of the myometrial defect

follow-up MRI showed a normal appearing uterus (Figure 6).

Written informed consent was obtained from the patient and her parents for both the surgical procedure and the publication of this case report, with approval of the Başkent University Non-Interventional Clinical Research Ethics Committee (approval number: 22/226, date: 28.12.2022).

Discussion

This case report illustrates ACUM, highlighting its symptoms, diagnostic evaluation (pelvic ultrasound and MRI), medical management, surgical excision, and follow-up. The initial physical examination revealed a mass on ultrasound and pelvic MRI consistent with ACUM. Medical treatment provided minimal relief, leading to laparoscopic resection. The patient's symptoms completely resolved following the excision.

ACUM is a rare Müllerian anomaly and is often difficult to diagnose preoperatively due to its infrequent occurrence and similarities to other pelvic conditions. In adolescents, severe cyclic dysmenorrhea, refractory to NSAIDs or COCs, should raise suspicion for Müllerian anomalies. The differential diagnosis should include pedunculated myomas, endometriomas, and para-ovarian cysts (6). Literature describes similar lesions under various names, including juvenile cystic adenomyoma, cystic adenomyoma, cystic adenomyosis, and accessory cavitated mass. The term ACUM is now preferred and has replaced the term "juvenile cystic adenomyoma" due to reflecting the nature of the condition more accurately, as described by Takeda et al. (7). Recently, Sachedina Parhar et al. (8) proposed the term "accessory uterine cavities" for this entity. Precise diagnosis depends on intraoperative and histopathological findings.

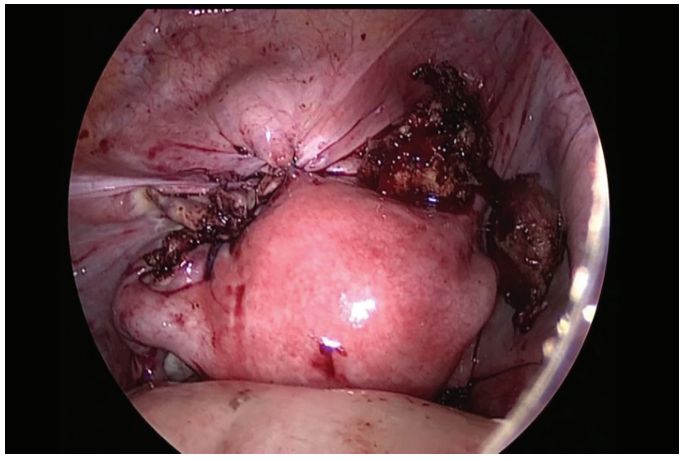

Figure 5. Final appearance of the uterus

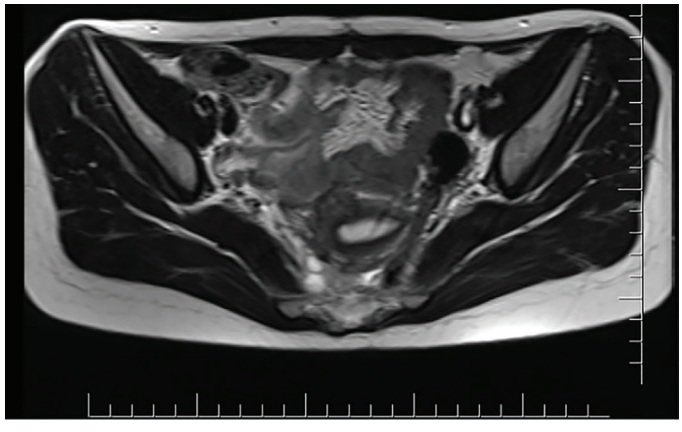

Figure 6. Magnetic resonance imaging image of the uterus after surgery

Our case meets the established diagnostic criteria for ACUM (3). While MRI can suggest the diagnosis, definitive confirmation requires surgical excision and histopathological examination (9). Video footage from the presented patient's surgery illustrates the drainage of chocolate-brown fluid, indicative of old blood, as previously reported (6). Histopathological analysis noted small foci of adenomyosis in the myometrium adjacent to the mass. Notably, our case differed from most reported cases of ACUM, which typically present on the right side of the uterus (10).

Conclusion

ACUM remains a rare form of Müllerian anomaly and is difficult to diagnose preoperatively despite advanced imaging techniques. Surgical excision performed through laparotomy or laparoscopy remains the definitive treatment. Laparoscopic procedures are associated with a lower complication rate and higher operative satisfaction (11). This aim of this report was to highlight this rare condition and so remind clinicians to consider Müllerian anomalies in this patient demographic. This report highlights the need to consider ACUM in the differential diagnosis of severe dysmenorrhea. It underscores the importance of including ACUM in the differential diagnosis and highlights the effectiveness of surgical excision for long term relief. Moreover, we offer a step-by-step video for ACUM excision. The complete resolution of our patient's symptoms without complications highlights the effectiveness and safety of the surgical approach.

Video 1.

http://dx.doi.org/10.4274/jtgga.galenos.2025.2025-10-5.video1

Ethics

Ethics Committee Approval: *This study was approved by the Başkent University Non-Interventional Clinical Research Ethics Committee (approval number: 22/226, date: 28.12.2022).*

Informed Consent: *Written informed consent was obtained from the patient and her parents for both the surgical procedure and the publication.*

Footnotes

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

Financial Disclosure: *The authors declared that this study received no financial support.*

References

1. Agarwal AK, Agarwal A. A study of dysmenorrhea during menstruation in adolescent girls. Indian J Community Med. 2010; 35: 159-64.
2. Deng F, Liu K, Huang Y, Chen Q, Wang L, Xiao X, et al. Successful treatment of a rare giant accessory cavitated uterine mass: a case report. J Int Med Res. 2024; 52: 3000605241252238.
3. Acién P, Bataller A, Fernández F, Acién MI, Rodríguez JM, Mayol MJ. New cases of accessory and cavitated uterine masses (ACUM): a significant cause of severe dysmenorrhea and recurrent pelvic pain in young women. Hum Reprod. 2012; 27: 683-94.
4. Grimbizis GF, Di Spiezio Sardo A, Saravelos SH, Gordts S, Exacoustos C, Van Schoubroeck D, et al. The Thessaloniki ESHRE/ESGE consensus on diagnosis of female genital anomalies. Gynecol Surg. 2016; 13: 1-16.
5. Garofalo A, Alemanno MG, Sochirca O, Pilloni E, Garofalo G, Chiadò Fiorio Tin M, et al. Accessory and cavitated uterine mass in an adolescent with severe dysmenorrhoea: from the ultrasound diagnosis to surgical treatment. J Obstet Gynaecol. 2017; 37: 259-61.
6. Paul PG, Chopade G, Das T, Dhivya N, Patil S, Thomas M. Accessory cavitated uterine mass: a rare cause of severe dysmenorrhea in young women. J Minim Invasive Gynecol. 2015; 22: 1300-3.
7. Takeda A, Sakai K, Mitsui T, Nakamura H. Laparoscopic management of juvenile cystic adenomyoma of the uterus: report of two cases and review of the literature. J Minim Invasive Gynecol. 2007; 14: 370-4.
8. Sachedina Parhar A, Mellor A, Moeed S, Grover SR. Accessory uterine cavities: a review of cases and an appeal for standard terminology. Fertil Steril. 2025; 123: 1101-13.
9. Bedaiwy MA, Henry DN, Elguero S, Pickett S, Greenfield M. Accessory and cavitated uterine mass with functional endometrium in an adolescent: diagnosis and laparoscopic excision technique. J Pediatr Adolesc Gynecol. 2013; 26: e89-91.
10. Acién P, Acién M, Fernández F, José Mayol M, Aranda I. The cavitated accessory uterine mass: a Müllerian anomaly in women with an otherwise normal uterus. Obstet Gynecol. 2010; 116: 1101-9.
11. Otten LA, Lama S, Otten JW, Winkler K, Ralser DJ, Egger EK, et al. Clinical comparison of laparoscopic and open surgical approaches for uterus-preserving myomectomy: a retrospective analysis on patient-reported outcome, postoperative morbidity and pregnancy outcomes. Arch Gynecol Obstet. 2025; 311: 1359-69.

Non-anatomical liver resection using Kelly clamp-crush technique during interval cytoreduction

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Abstract

Ovarian cancer is frequently diagnosed at an advanced stage, with liver metastases commonly observed, adversely affecting prognosis. Achieving complete cytoreduction (R0) is essential for improving overall survival in advanced ovarian cancer. Liver resections, particularly for isolated and resectable lesions, have demonstrated survival benefits. Non-anatomical resections, while preserving functional liver parenchyma, are increasingly employed in this context. This study showcases a surgical video illustrating a non-anatomical wedge liver resection performed for oligometastatic disease as part of interval cytoreductive surgery in advanced-stage ovarian cancer. A young multiparous woman in her 30 s with high-grade serous carcinoma of the right ovary and multiple hepatic metastases at diagnosis had a persistent dominant residual liver lesion following neoadjuvant chemotherapy. She had undergone prior right salpingo-oophorectomy. Interval cytoreductive surgery included peritoneal wash for cytology, hysterectomy with excision of left tube and ovary, retroperitoneal lymph node sampling, total omentectomy, peritoneal deposit excision, and non-anatomical liver resection. The surgical peritoneal cancer index was 7. Intra-operative ultrasound guided localization of a 2.5×2 cm intraparenchymal lesion in liver segments IVB/V. Wedge resection with adequate margins was performed using the Kelly clamp-crush technique, LigaSure, and monopolar cautery after ligation of the distal middle hepatic vein. The postoperative recovery proceeded without complications. Metastatic carcinoma in the liver lesion and peritoneal deposit, with no residual disease in other specimens were reported from histology. The patient received three cycles of adjuvant chemotherapy and remains disease-free at 18 months of follow-up. Non-anatomical liver resections are feasible and safe in advanced ovarian cancer with resectable oligometastatic hepatic disease and should be integrated into cytoreductive surgery when indicated. While recent evidence supports the safety and survival benefits of liver resections, additional research is needed to clarify their prognostic significance in advanced ovarian cancer. [J Turk Ger Gynecol Assoc. 2026; 27(3): 226-8]

Keywords: Advanced ovarian cancer, liver metastasis, non-anatomical liver resection, cytoreductive surgery, oligometastatic disease

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Introduction

Ovarian cancer is identified at advanced stages The International (Federation of Gynecology and Obstetrics stage IIIC-IV) in 60-80% of cases, often necessitating visceral organ resections to attain optimal cytoreduction. Among metastatic sites, the liver is one of the most commonly affected and is associated with a poor prognosis. At present, the negative correlation between residual tumor after cytoreduction and overall survival is universally acknowledged, and liver resection appears to offer a survival advantage for patients with ovarian cancer liver metastases.

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DOI: *10.4274/jtgga.galenos.2026.2024-11-14*

Cite this article as: *Heda A, Rajaram S, Rakesh NR, Chowdhury N. Non-anatomical liver resection using Kelly clamp-crush technique during interval cytoreduction. J Turk Ger Gynecol Assoc. 2026; 27(3): 226-8*

Liver resection is indicated in cases where complete resection (R0) extrahepatic cytoreduction can be achieved and when there is an isolated, resectable liver lesion (1). Key considerations for planning hepatic resection include the location, distribution, and number of tumor lesions, as well as the involvement of vascular and biliary structures. Additional factors include assessing the quality of functional liver parenchyma, ensuring adequate vascular supply, and maintaining proper biliary drainage in the residual liver following hepatectomy. Although anatomical liver resections lead to decreased blood loss, non-anatomical resection has greater parenchyma sparing potential (2). Studies have shown that cases with *BRCA* mutations have higher risk of liver metastasis but better survival vis-à-vis women with *BRCA* wild type after liver resection (3). Liver resection has been found to be safe and feasible in advanced ovarian cancer from primary up to quaternary cytoreduction with survival benefits (4).

Case report

A stepwise surgical demonstration of wedge liver metastasectomy integrated into interval cytoreductive management of advanced ovarian carcinoma with oligometastatic hepatic spread.

A multiparous female patient in her 30s, with Eastern Cooperative Oncology Group performance status 1 and body mass index of 31.2 kg/m^2, was diagnosed with stage IVB high-grade serous carcinoma of the right ovary. She initially underwent right salpingo-oophorectomy with omental biopsy at an outside center. Histopathological review confirmed high-grade serous adenocarcinoma. Subsequent contrast-enhanced computed tomography revealed multiple hepatic metastases. Germline *BRCA1/2* mutation testing was negative.

The patient received four cycles neoadjuvant chemotherapy with paclitaxel and carboplatin, following which interval imaging demonstrated a reduction in the hepatic disease burden, with a persistent residual hepatic lesion. Following multidisciplinary evaluation, she was planned for interval cytoreductive surgery.

Exploratory laparotomy was performed as part of interval cytoreduction. Following peritoneal washings for cytological assessment, total abdominal hysterectomy with left salpingo-oophorectomy, pelvic lymph node debulking, total omentectomy, and excision of a 2×2 cm subdiaphragmatic peritoneal deposit adjacent to liver segment VI were undertaken. The surgical peritoneal cancer index was 7.

Intra-operative ultrasonography was used to accurately localize a 2.5×2 cm intraparenchymal metastatic lesion involving liver segments IVB/V (Figure 1). After delineating adequate resection margins, non-anatomical wedge liver resection was performed using the Kelly clamp-crush technique in combination with LigaSure and monopolar cautery following ligation of the distal middle hepatic vein(Figure 2). Complete gross cytoreduction was achieved (Figure 3).

Discussion

The post-operative recovery was smooth and without complications. The histopathology report confirmed a metastatic carcinoma in the liver lesion and peritoneal deposit while the rest of the specimens showed no residual disease. Negative surgical margins of the liver specimen were confirmed on histopathological assessment, establishing an R0 resection. Three cycles of adjuvant chemotherapy were administered and the patient is disease free for 18 months and on follow-up at the time of writing.

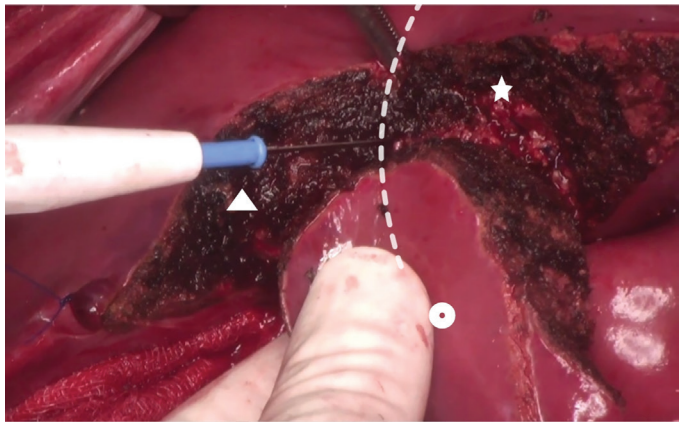

Figure 1. Transection of segment IVB/V of liver with liver metastasis (dotted line, Cantlie's line; star, segment IVB; triangle, segment V; circle, intraparenchymal deposit with 1 cm margin)

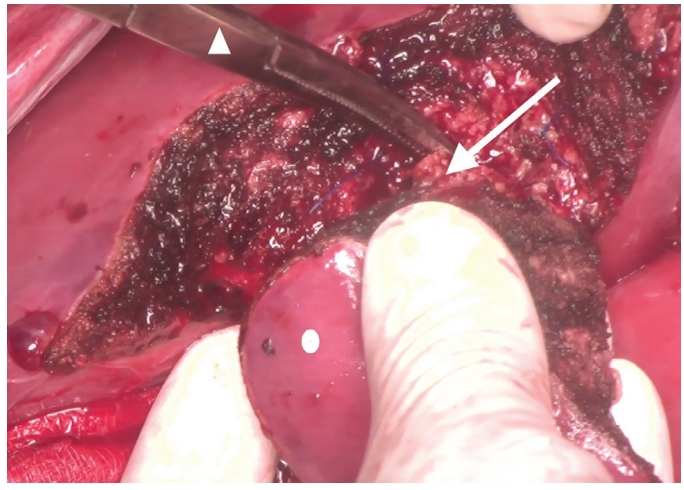

Figure 2. Kelly clamp used to crush the liver parenchyma and identify the underlying vessels (triangle, Kelly clamp; circle, excised liver lesion; arrow, distal middle hepatic vein)

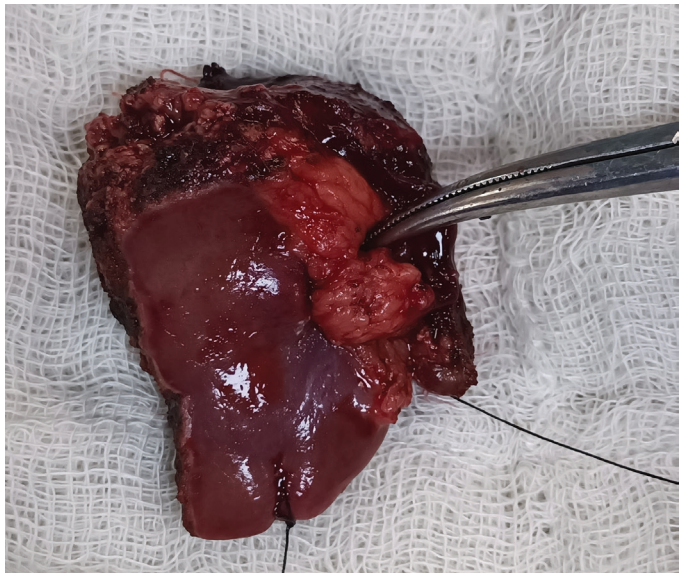

Figure 3. Post-operative specimen for liver segment with 1 cm margin

Conclusion

Non-anatomical liver resection should be integrated into cytoreductive surgical strategies, particularly for cases involving surgically accessible oligometastatic disease. Recent systematic reviews have demonstrated the feasibility and safety of liver resection in such settings. However, additional research is essential to better understand its long-term prognostic implications.

Video 1.

http://dx.doi.org/10.4274/jtgga.galenos.2026.2024-11-14.video1

Ethics

Ethics Committee Approval: *The ethics committee approval was obtained from Institutional Ethics Committee, All India Institute of Medical Sciences, Rishikesh (AIIMS/IEC/24/62) dated 19/01/2024.*

Informed Consent: *The authors confirm that written informed consent for publication have been obtained from the involved patients.*

Footnotes

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

Financial Disclosure: *The authors declared that this study received no financial support.*

References

1. Forte S, Ferrari F, Valenti S, Capozzi VA, Santana BN, Babin G, et al. Liver surgery for advanced ovarian cancer: a systematic review of literature. European Journal of Gynaecological Oncology. 2022; 43: 64-72.
2. Braunwarth E, Stättner S, Fodor M, Cardini B, Resch T, Oberhuber R, et al. Surgical techniques and strategies for the treatment of primary liver tumours: hepatocellular and cholangiocellular carcinoma. Eur Surg. 2018; 50: 100-12.
3. Zhao H, Xu F, Li J, Ni M, Wu X. A population-based study on liver metastases in women with newly diagnosed ovarian cancer. Front Oncol. 2020; 10: 571671.
4. Luna-Abanto J, García Ruiz L, Laura Martinez J, Álvarez Larraondo M, Villoslada Terrones V. Liver resection as part of cytoreductive surgery for ovarian cancer. J Gynecol Surg. 2020; 36: 70-5.

Laparoscopic repair of a proximal ureteral injury during transperitoneal para-aortic lymphadenectomy: a video article

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Abstract

Ureteral injury during advanced gynecologic laparoscopic procedures is an uncommon but potentially serious complication, particularly during para-aortic lymphadenectomy performed for oncologic staging. We describe the laparoscopic management of a proximal right ureteral transection encountered during transperitoneal para-aortic lymphadenectomy in a 56-year-old woman (body mass index 36 kg/m^2) with high-risk endometrial carcinoma. The injury was recognized intraoperatively and repaired using a tension-free ureteroureterostomy over a double-J stent. Key technical steps, including exposure in obese patients and preservation of ureteral vascularity, are demonstrated. This report highlights that timely intraoperative recognition and laparoscopic repair of proximal ureteral injury can prevent major morbidity and obviate open surgery, emphasizing the importance of advanced, minimally invasive surgical expertise. [J Turk Ger Gynecol Assoc. 2026; 27(3): 229-30]

Keywords: Ureteral injury, para-aortic lymphadenectomy, laparoscopy, endometrial cancer, ureteroureterostomy

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Introduction

Ureteral injury is an uncommon but serious complication of gynecologic laparoscopic surgery, with a reported incidence ranging from 0.2% to 6.0% depending on procedure type and patient characteristics (1). Such injuries carry the risk of delayed diagnosis, prolonged morbidity, and potential loss of renal function (2). In the context of endometrial cancer staging, para-aortic lymphadenectomy is an essential component for patients at high-risk of lymphatic spread and can be performed via either transperitoneal or extraperitoneal approaches (3).

The transperitoneal route offers advantages, such as early uterine removal and intraoperative frozen-section analysis, enabling tailored lymphadenectomy. However, this approach presents technical challenges, particularly regarding bowel retraction and exposure of retroperitoneal structures. Delayed recognition of ureteral injury is associated with increased morbidity and impaired renal outcomes, whereas prompt intraoperative identification and minimally invasive repair may be facilitated by advanced surgical expertise, thus improving postoperative recovery and outcome.

Herein, we describe the laparoscopic management of a proximal ureteral transection encountered during transperitoneal para-aortic lymphadenectomy, focusing on technical considerations for safe exposure, early recognition, and immediate repair. This report was prepared in accordance with the SCARE 2025 guideline (4).

Case report

Intraoperative frozen-section analysis revealed upgrading of the tumor measuring 8×4 cm at its maximum diameter to grade 3 with deep myometrial invasion. According to the ESMO-ESGO-ESTRO consensus classification, the patient was categorized as high-risk, and pelvic and para-aortic lymphadenectomy was subsequently performed.

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DOI: *10.4274/jtgga.galenos.2026.2026-2-11*

Cite this article as: *Hanedan C, Köksal OK, Öncü HN, Zengin Aksel T, Korkmaz V. Laparoscopic repair of a proximal ureteral injury during transperitoneal para-aortic lymphadenectomy: a video article. J Turk Ger Gynecol Assoc. 2026; 27(3): 229-30*

During meticulous retroperitoneal inspection, a proximal transection of the right ureter was identified intraoperatively. Dense perirenal adipose tissue and restricted working space increased the technical difficulty of exposure. Both ureteral ends were carefully mobilized to preserve vascularity and allow a tension-free end-to-end anastomosis. A continuous ureteroureterostomy was performed using a 4-0 absorbable suture over a 4.8-Fr double-J ureteral stent. The key steps of intraoperative recognition and laparoscopic repair are demonstrated in Video 1.

The total operative time was 180 minutes, with an estimated blood loss of approximately 100 mL. Anastomotic integrity was confirmed intraoperatively by visualization of urine flow and was verified by postoperative imaging. The patient was discharged on postoperative day 6 without complications and remained asymptomatic at 16 months of follow-up.

Discussion

Prompt recognition and immediate repair of ureteral injury are important for minimizing morbidity and preserving renal function. Previous series have demonstrated that ureteral injuries identified intraoperatively can be successfully managed when addressed without delay (2). Reported risk factors include visceral obesity and the use of energy devices near perirenal fat, highlighting the importance of strict adherence to anatomical landmarks during para-aortic dissection (1,5).

Surgical repair techniques vary according to the location and extent of injury. While ureteroneocystostomy remains the most reported reconstructive option, ureteroureterostomy is appropriate in selected cases with short defects, well-vascularized ureteral ends, and the ability to achieve a tension-free anastomosis (5). When performed laparoscopically by experienced surgeons, outcomes are comparable to open repair while offering reduced postoperative pain and faster recovery (6).

The present experience demonstrates that a proximal ureteral transection occurring during transperitoneal para-aortic lymphadenectomy may be managed laparoscopically without conversion to open surgery, even in technically demanding settings such as visceral obesity. The accompanying surgical video illustrates practical steps for exposure, early recognition, and precise suturing, providing an educational resource for surgeons confronted with similar intraoperative complications.

In specialized gynecologic oncology centers, formal training in advanced retroperitoneal dissection facilitates immediate laparoscopic repair of ureteral injuries when they are encountered. Postoperative urologic follow-up remains essential to ensure long-term functional success.

Conclusion

Although ureteral injury during laparoscopic para-aortic lymphadenectomy is uncommon and should be avoided if at all possible, when it occurs it represents a technically demanding complication requiring prompt recognition and advanced laparoscopic skills. This report demonstrated that proximal ureteral transections may be successfully repaired laparoscopically through a tension-free ureteroureterostomy, avoiding conversion to open surgery. In centers with sufficient expertise, minimally invasive repair represents a reliable alternative to traditional open management with favorable postoperative outcomes.

Video 1.

http://dx.doi.org/10.4274/jtgga.galenos.2026.2026-2-11.video1

Ethics

Ethics Committee Approval: *Institutional review board approval was waived because this study is a single-case video article and does not involve research on human subjects.*

Informed Consent: *Written informed consent was obtained from the patient for publication of the case details and accompanying video/images.*

Footnotes

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

Financial Disclosure: *The authors declared that this study received no financial support.*

References

1. Kobayashi H, Kobayashi M, Takaki Y, Kondo Y, Hamada Y, Shimizu H, et al. Ureter injury in laparoscopic para-aortic lymphadenectomy for endometrial cancer by the transperitoneal approach. Case Rep Obstet Gynecol. 2023; 2023: 3138683.
2. Chan JK, Morrow J, Manetta A. Prevention of ureteral injuries in gynecologic surgery. Am J Obstet Gynecol. 2003; 188: 1273-7.
3. Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, et al; ESMO-ESGO-ESTRO Endometrial Consensus Conference Working Group. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up. Ann Oncol. 2016; 27: 16-41. Erratum in: Ann Oncol. 2017; 28: iv167-iv168.
4. Kerwan A, Al-Jabir A, Mathew G, Sohrabi C, Rashid R, Franchi T, et al. Revised Surgical Case Report (SCARE) guideline: an update for the age of artificial intelligence. Premier Journal of Science. 2025: 10; 100079
5. Martin A, Wells A, Anderson ML, Chern JY, Rutherford TJ, Shahzad MM, et al. Trends in ureteral surgery on an academic gynecologic oncology service. Gynecol Oncol. 2021; 163: 552-6.
6. Arcieri M, Cuman M, Restaino S, Tius V, Cianci S, Ronsini C, et al. Exploring urinary tract injuries in gynecological surgery: current insights and future directions. Healthcare (Basel). 2025; 13: 1780.

CONGRESS CALENDAR

INTERNATIONAL MEETINGS

(for detailed International Meeting please go website: https://www.emedevents.com/obstetrics-and-gynecology)

September 06-09, 2026	36th ISUOG World Congress, Dubai, UAE
October 04-07, 2026	ESGE 35th Annual Congress, Krakow, Poland
October 24-28, 2026	American Society for Reproductive Medicine (ASRM) 82nd Annual Meeting, Baltimore, USA
November 12-14, 2026	The 34th World Congress on Controversies in Obstetrics Gynecology & Infertility (COGI), Athens, Greece
November 13-16, 2026	The 55th American Association of Gynecologic Laparoscopists (AAGL) Global Congress on Minimally Invasive Gynecologic Surgery (MIGS), Boston, USA
April 28-May 2, 2027	16th Turkish-German Gynecology Congress, Antalya, Türkiye

CONGRESS CALENDAR

NATIONAL MEETINGS

(for detailed National Meeting please go website: https://www.kongreuzmani.com/2026)

September 24-27, 2026	5. Tüp Bebek ve İnfertilite Derneği Kongresi, Girne, K.K.T.C
September 30-October 4, 2026	8. Jinekoloji ve Obstetrikte Tartışmalı Konular Kongresi, Antalya, Türkiye
October 28-31, 2026	Türkiye Maternal Fetal Tıp ve Perinatoloji Derneği 15. Ulusal Kongresi, Antalya, Türkiye
October 28-November 1, 2026	13. Üreme Tıbbı ve Cerrahisi Derneği Kongresi, Antalya, Türkiye
October 30-November 1, 2026	13. Uluslararası Pelviperineoloji ve Fonksiyonel Kozmetik Jinokoloji ve Üroloji Kongresi, İstanbul, Türkiye
November 19-22, 2026.	14. Türk Üreme Sağlığı ve İnfertilite Vakfı Kongresi, Antalya, Türkiye