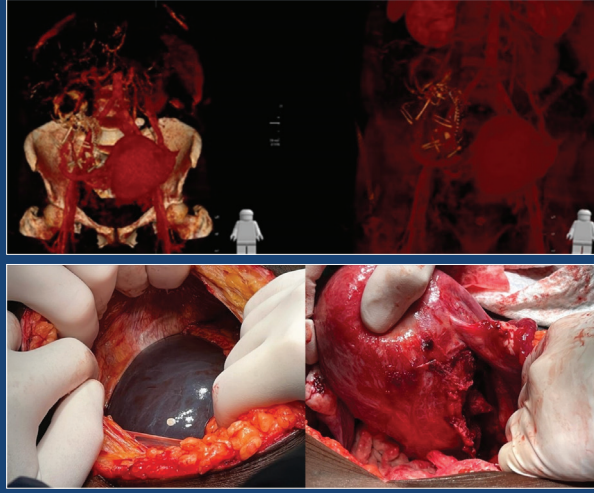




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Cover Picture: Algeri et al. Asymptomatic uterine rupture

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Journal of the Turkish-German Gynecological Association

Editorial



Dear Colleagues,

It is my great pleasure to introduce the last issue of the “Journal of the Turkish-German Gynecological Association (J Turk Ger Gynecol Assoc)” in the publishing year of 2023. This issue is consisted of seven articles and one review that we hope you will read with interest. Here we share some of our favorite articles that were published in this issue of the journal.

Unexpected placental adhesion at the site of implantation is referred to as the placenta accreta spectrum (PAS). There is variation in the reported incidence of PAS among women who have had prior cesarean deliveries, ranging from 0.91% to 1 in 313. Severe and occasionally fatal bleeding can result in maternal morbidity and death. To optimize the outcomes, antenatal diagnosis of PAS is particularly beneficial. You will get the occasion to read an article about the function of Doppler ultrasound in pregnant women with PAS.

One of the most prevalent hormonal problem affecting women of childbearing age is polycystic ovary syndrome (PCOS). The effects of several dietary supplements and herbal extracts on anthropometric, metabolic, and androgenic indicators in PCOS have been studied in a number of RCTs. You will have the chance of reading a systematic review comparing the effectiveness of several nutritional supplements and herbal extracts in regulating body mass index, waist circumference, androgenic indicators, blood glucose and lipid metabolism markers.

Dear Esteemed Researchers and Reviewers,

The annual number of scientific articles published exceeds 2.5 million, and this number is increasing rapidly. We’ve delivered excellent research to make progress in the field with your assistance. We acknowledge that your scientific achievements will have a significant impact on life-saving measures or raising standards of living.

As you may already be aware, our journal received its first impact factor, 1.4, in June 2023 since it is listed in the Clarivate’ Emerging Sources Citation Index (ESCI)! In this sense, we would like to express our gratitude to each and every one of the reviewers, who played a critical role in this accomplishment. Along with this information, we hope that our open publication approach will inspire more researchers to submit their work to JTGGGA so they can gain from a large readership and high-quality peer review.

Please visit us online at www.jtggga.org and keep in touch with us by following us on Twitter @JtgggaOfficial. I would like to wish you a happy new year in 2024 and we are looking forward to receiving your valuable submissions, thank you in advance for your contributions.

Sincerely,

Prof. Cihat Ünlü, M.D.

Editor in Chief of J Turk Ger Gynecol Assoc

President of TGGF

Novel markers of Doppler ultrasonography in the placenta accreta spectrum to predict complications

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Abstract

Objective: Ultrasonography (US) is an acceptable tool to diagnose the placenta accreta spectrum (PAS) among pregnant women. However, the lack of a robust criteria for diagnosis and predicting the severity of the consequences facing pregnant women requires identification of novel biomarkers.

Material and Methods: This prospective, cross-sectional study was performed on pregnant women with a probable diagnosis of PAS. Their demographic information, medical and surgical history, blood loss severity (severe ≥ 2500 mL) following hysterectomy, and the histopathology after the surgery were collected. In addition, the Doppler imaging of both uterine arteries, including the pulsatility index, resistance index, peak systolic velocity (PSV), the PSV of the posterior part of the bladder, cervix, the largest lacuna, and the posterior lacuna of the bladder were calculated by Doppler US. Data were analyzed to investigate the relationship between Doppler markers and the severity of PAS in terms of bleeding, hysterectomy, and histopathology.

Results: Fifty-one women were enrolled with a mean age of 35.4 ± 4.11 years and 17 (33.3%) had severe bleeding. There were significant differences between median (range) bladder PSV [57 (34-90) vs. 33 (20-64); $p < 0.001$], cervix PSV [26 (0-63) vs. 18 (0-76); $p = 0.04$] and left uterine artery [89 (81-135) vs. 68 (61-113); $p = 0.045$] for women with and without severe bleeding, respectively. Thirty-four (66.66%) had hysterectomy. Comparison of bladder PSV, cervix PSV, and left uterine PSV for women with and without hysterectomy were 46 (20-90) vs. 39.5 (33-46) ($p = 0.005$), 20 (0-76) vs. 20 (14-26) ($p = 0.013$) and 68 (61-135) vs. 82 (63-101) ($p = 0.003$), respectively.

Conclusion: Bladder PSV, cervix PSV, and uterine PSV were significantly higher in pregnant women with PAS, and they may be useful diagnostic and prognostic markers. (J Turk Ger Gynecol Assoc 2023; 24: 228-34)

Keywords: Doppler ultrasonography, hysterectomy, hemorrhage, PAS, placenta accreta spectrum, PSV

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Introduction

The placenta accreta spectrum (PAS) refers to unexpected adherence of the placenta to its implantation site. It includes accreta, increta, and percreta types. The pathoetiology is unknown but placenta previa and earlier uterine surgery have been reported to be significant risk factors for the condition (1,2). The rate of cesarean delivery, a relatively common uterine surgery, is increasing in many countries and this has been associated with an increase in the rate of PAS (3). The reported incidence of PAS is variable ranging from 0.91% (4) to 1 in 313 women with previous cesarean delivery (5). Obstetric bleeding and surgical issues, such as hysterectomy, are significant complications facing women with PAS. Furthermore, post-traumatic stress disorder, other psychological complications, and more prolonged hospital admission may occur among pregnant women with PAS (6).

Histopathology is the gold standard for diagnosing PAS (2) but ultrasonography (US) is common in diagnosing and evaluating the severity of the complications facing pregnant women. However, US is insufficient, especially in pregnant women with the posterior placenta (7). Magnetic resonance imaging may be an appropriate choice for pregnant women with PAS in whom evaluation is difficult with US (8).

In 2021 the Society for Maternal-Fetal Medicine (SMFM) suggested different sonographic markers for PAS for each trimester, such as cesarean scar and low implantation pregnancy in first trimester, placental lacuna, abnormal uteroplacental interface, abnormal uterine contour (placental bulge) and exophytic mass (9).

Doppler US is a method based on differences in ultrasound frequency when an object is moving and is a safe imaging method in pregnancy (10). Collins et al. (11) reported that markers produced during three-dimensional (3D) color Doppler sonography were effective for diagnosing PAS, and may be able to predict the severity. Moreover, Hussein et al. (12) showed that specific markers in 2D and 3D Doppler were able to predict the severity and consequences of hysterectomy and bleeding in pregnant women with PAS disorders. The SMFM considered bridging vessels (blood vessels lengthened from the placenta across the myometrium) as a Doppler US marker for PAS. Currently, the role of Doppler US for diagnosis of PAS is a research gap and requires more study to clarify (9). In the present study, the aim was to investigate the role of Doppler US in pregnant women with PAS, specifically to identify and assess novel biomarkers using this modality that had diagnostic utility in identifying and predicting the severity of PAS. This will allow clinicians to choose the appropriate procedures to decrease morbidities and mortality among pregnant women with PAS.

Material and Methods

After Research Ethics Committees of Imam Khomeini Hospital Complex-Tehran University of Medical Sciences approval, this prospective cross-sectional study was performed in a tertiary referral center from September 2021 to August 2022 (approval number: IR.TUMS.IKHC.REC.1400.201, date: 01.09.2021). The study population was pregnant women with a suspicion of PAS. Women were referred to this center, after confirmation of likely PAS by two experienced experts and registering the PAS referral criteria were recorded. Informed consent was obtained from all participants for inclusion in the study. First, participants' demographics and medical history were collected, including obstetrics, abortion, medical and surgical history. In addition, history of cesarean section and reasons, history of gynecological and/or uterine surgery (especially myomectomy), and history of cesarean scar pregnancy were recorded. The study excluded women with severe anemia, coagulopathies, emergency status, and severe bleeding before delivery, such as placenta abruption.

One expert perinatal fellow performed the sonography using a Philips affinity 70 system before the surgery based on accreta in familial mediterranean fever. The sonography was performed transabdominally by positioning the probe vertically without pressure on the pubic symphysis with a full bladder. After locating the placenta and associated structures, Doppler assessment of the right and left uterine arteries, including the pulsatility index, resistance index (RI), and peak systolic velocity (PSV) were calculated. In addition, the PSV of the posterior part of the bladder, cervix, the largest lacuna, and the posterior lacuna of the bladder were measured. During uterine Doppler measurement, the probe was positioned parallel to the woman's sagittal axis (parasagittal) and perpendicular to the location of the bladder.

All pregnant women in this study delivered electively between 34 to 37 weeks of gestational age, based on placental position, especially placenta previa, the severity of accreta, and pregnant women's symptoms, including hematuria. All cesarean sections were performed by two expert surgeons, who also undertook hysterectomies in cases of uncontrolled bleeding when the uterus could not be preserved. In addition, all abdominal incisions were performed using Maylard incisions, and myometrial incisions were vertical in the cases of the placenta previas and Kerr in non-previa types.

Weighing drain sheets and gauzes before and after the surgery was used to calculate the average blood loss for each pregnant woman. In order to avoid miscalculation of blood loss by amniotic fluid (AF) contamination, AF was gathered in another suction. In the present study, massive bleeding was defined as blood loss of ≥ 2500 cc or requiring >3 units packed red blood

cells during the operation (12). Other morbidities, such as hysterectomy and admission duration, were documented. In the present study, accreta was classified as type 1 accreta and increta and percreta were classified as type 2 accreta, being more invasive based on pathologic reports (13).

The primary outcome was the relationship between the Doppler findings and massive bleeding. The secondary outcome was the relationship of the Doppler findings with the need for a hysterectomy, type of accreta, and other surgical morbidities, such as bladder and ureteral injury, intensive care unit admission, relaparotomy, and readmission.

Ethical statement

In implementing all stages of the study, privacy protection and confidentiality of the information obtained from files and other processes were considered. To preserve the pregnant women's information and the researchers blinding to the participants, a code was assigned to each pregnant woman, and used in all stages of registration. Data and analyses were performed using these codes.

Statistical analysis

All data were analyzed using SPSS, version 22 (IBM Inc., Armonk, NY, USA). A p-value less than 0.05 was considered significant. Mean ± standard deviation, median (minimum-maximum) were obtained for quantitative data. Also, frequency and relative frequency were obtained for qualitative data. The Kolmogorov-Smirnov test was used to assess normality of data distribution. All quantitative variables in this study had non-normal distribution. Therefore, Mann-Whitney test was used to investigate the relationship between quantitative variables and massive bleeding, hysterectomy, and pathology outcomes. The chi-square test was used to investigate the relationship between groups and categories for qualitative variables. Finally, receiver operating characteristic (ROC) curve was performed for variables and showed their specificities and sensitivities as prognostic parameters for PAS.

Results

Fifty-one pregnant women were included (Figure 1) with a mean age of 35.4±4.1 years and 34.4±2.1 weeks gestation (median: 28.0) at sonography. Their mean body mass index was 28.3±3.5 kg/m² and their mean admission was 4.15±1.1 days. Three (5.9%) women had no previous C/S with only a history of myomectomy, 31 (60.8%) had previous elective C/S, and 17 (33.3%) had previous emergent C/S in the non-active phase of labor. None of them had emergent C/S in the active phase of labor. In addition, 8 (15.7%) had a previous history of abortion (Table 1).

Surgical complications included one with a ureter injury during the operation (percreta case with parametrial involvement that was repaired via surgery). In addition, one had hematuria after the surgery, controlled by cystoscopy and bleeding vessel coagulation in the bladder. There was no laparotomy requirement in the study.

Bleeding

Severe bleeding occurred in 17 (33.3%). The median bladder PSV associated with women with severe bleeding was 57

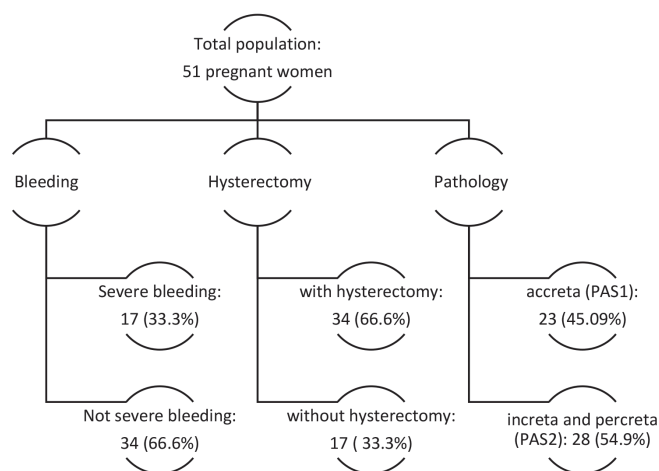


Figure 1. The flow chart of the population study
PAS: Placenta accreta spectrum

Table 1. The characteristic information of the pregnant women

Age (years)	35.4±4.11*; 35.00 (27, 48)**
Gestational age (weeks)	34.4±2.14*; 28.00 (18, 38)**
No previous C/S with only a history of myomectomy	3 (5.8%)***
History of emergent C/S	18 (35.29%)***
History of elective C/S	31 (60.78%)***
Previous surgery on the uterine	4 (7.84%)***
BMI (kg/m ²)****	28.33±3.53*; 27.75 (22, 39)**
Admission days (days)	4.15±1.12*; 4 (2, 14)**
History of abortion	8 (15.68%)***
Type of PAS*****	
PAS1	23 (45.09%)***
PAS2	28 (54.9%)***
Hysterectomy after surgery	34 (66.66%)***
Severe blood loss	17 (33.33%)***

*: Mean ± standard deviation, **: Median (minimum, maximum), ***: Number (%), ****: Body mass index, *****: Accreta: PAS1, and increta and percreta: PAS2, BMI: Body mass index, PAS: Placenta accreta spectrum

(34-90) which was significantly greater ($p < 0.001$) than in women without severe bleeding at 33 (20-64).

The median of cervical PSV among women with severe bleeding was 26 (0-63) while this was 18 (0-76) among women without severe bleeding ($p = 0.037$). The median PSV of the left uterine artery in those with severe bleeding was 89 (81-135) which was again significantly greater than in those without severe bleeding at 68 (61-113; $p = 0.045$).

The PSV of the higher vessels between the bladder and cervix was compared at the highest PSV value for each individual patient. The median of this PSV for women with severe bleeding was 57.5 (34-90) while it was 34 (20-76) for women without severe bleeding ($p < 0.001$). All measures by Doppler US compared pregnant women with/without severe bleeding are demonstrated in Table 2. Also, Figure 2 shows the appearance of markers on Doppler US.

Hysterectomy

Hysterectomy was performed for 34 (66.7%) women. The median bladder PSV among women who had a hysterectomy was 46 (20-90), compared to 39.5 (33-46) among women who had not had a hysterectomy after their delivery ($p = 0.005$). After delivery, women who had a hysterectomy demonstrated a cervical PSV of 20 (0-76) compared to 20 (14-26) among women without hysterectomy ($p = 0.013$). The median PSV of the left uterine artery among pregnant women who had a hysterectomy after their delivery was 68 (61-135), while it was 82 (63-101) among pregnant women without hysterectomy ($p = 0.003$).

The median PSV of the right uterine artery in pregnant women who underwent hysterectomy after delivery was 70 (51-125) while this was 82.5 (77-88) among pregnant women without hysterectomy ($p = 0.010$).

The mean PSV of the two uterine arteries was calculated. The median of these mean PSVs in women who underwent hysterectomy was 71.5 (59-110) while it was 82.25 (70-94) among those who had not had a hysterectomy ($p = 0.001$). Moreover, the median of the highest PSV measured in women who had a hysterectomy was 46 (20-90) compared to 39.5 (33-46) among women without hysterectomy ($p = 0.008$). All measures by Doppler US compared pregnant women with/without hysterectomy are demonstrated in Table 3.

Histopathological assessment

All patients were confirmed to have PAS by histopathology. Subtype breakdown was 23 (45.1%) type 1 PAS and 28 (54.9%) type 2 PAS. Women with type 1 PAS had a median bladder PSV of 32 (20-64) while those with type 2 PAS had 46 (27-90) ($p < 0.001$). The median cervical PSV in women with type 1 PAS was 18 (0-38), while it was 25 (0-76) for women with type 2 PAS ($p = 0.053$). In type 1 PAS the median PSV of the left uterine artery was 68 (61-113) and the same parameter in type 2 PAS was 77 (61-135) ($p = 0.049$). In type 1 PAS the median of the highest PSV was 32 (20-64) and this was 46 (27-90) in patients with type 2 PAS ($p < 0.001$). All measures by Doppler US compared between pregnant women and the type of pathology are demonstrated in Table 4.

Table 2. The Doppler markers and blood loss among pregnant women

	Severe blood loss (≥2500 mL)	No severe blood loss (<2500 mL)	Total	p-value
Number (%)	17 (33.33%)	34 (66.66%)	51.00 (100%)	
Bladder PSV	57.0 (34, 90)	33.00 (20, 64)	41.00 (20.90)	<0.001
Cervix PSV	26.0 (0, 63)	18.00 (0, 76)	20.00 (0.76)	0.037
The largest lacuna PSV	0.00 (0, 23)	0.00 (0, 41)	0.00 (0.41)	0.56
The posterior lacuna of the bladder PSV	0.00 (0, 31)	0.00 (0, 35)	0.00 (0.35)	0.773
The left uterine artery PSV	89.00 (81, 135)	68.00 (61, 113)	72.00 (61, 136)	0.045
The right uterine artery PSV	75.00 (60, 110)	73.50 (51.7, 127.0)	74.00 (51.7, 127.0)	0.298
The mean uterine artery PSV	81 (60, 110)	71.25 (59, 107)	73.25 (59, 110)	0.093
The highest PSV	57.50 (34, 90)	34.00 (20, 76)	41.50 (20, 90)	<0.001
The left uterine artery PI	0.90 (0.60, 1.36)	0.77 (0.55, 1.77)	0.79 (0.55, 1.77)	0.453
The right uterine artery PI	0.91 (0.58, 76.00)	0.87 (0.54, 66.00)	0.89 (0.54, 76.00)	0.555
The mean PI of the uterine artery	0.91 (0.63, 38.45)	0.88 (0.55, 33.30)	0.89 (0.55, 38.45)	0.075
The left uterine artery RI	0.56 (0.39, 1.00)	0.49 (0.40, 0.75)	0.51 (0.39, 1.00)	0.222
The right uterine artery RI	0.53 (0.40, 0.66)	0.51 (0.40, 0.68)	0.51 (0.40, 0.68)	0.302
The mean RI of the uterine artery	0.53 (0.44, 0.74)	0.50 (0.41, 0.68)	0.41 (0.41, 0.74)	0.110
All data are demonstrated in median (minimum, maximum), PSV: Peak systolic velocity, PI: Pulsatility index, RI: Resistance index				

Receiver operating characteristic curve

In the ROC curve (Figure 3), the cut-off identified for bladder PSV was 41, with a sensitivity of 84% and specificity of 60% (p<0.001). Furthermore, the cut-off of cervix PSV was 18.5 with 84% sensitivity and 57% specificity (p<0.001). The cut-off associated with the highest PSV was 38.8, with 84% sensitivity and 60% specificity (p=0.033) (Table 5). However, the best cut-off for the mean PSV of the uterine arteries was 66.7, with 83% sensitivity and 15% specificity, which was not sufficiently distinctive (p=0.110).

Discussion

Evaluating methods and biomarkers, including laboratory values, US findings and measures, and demographic and clinical information, are being investigated to identify the optimal assessment protocol for diagnosis and prognosis of PAS. Chong et al. (14) reported an in-house US scoring was a suitable tool to predict the prognosis of the PAS, such as hysterectomy requirement and severe bleeding. Marsoosi et al. (15) suggested that the scoring system, including several simple ultrasound and clinical characteristics, could effectively predict the prognosis and severity of the PAS when combined with appropriate clinical judgment. The present study demonstrated that Doppler US measurements may be useful as biomarkers to clarify the severity of PAS.

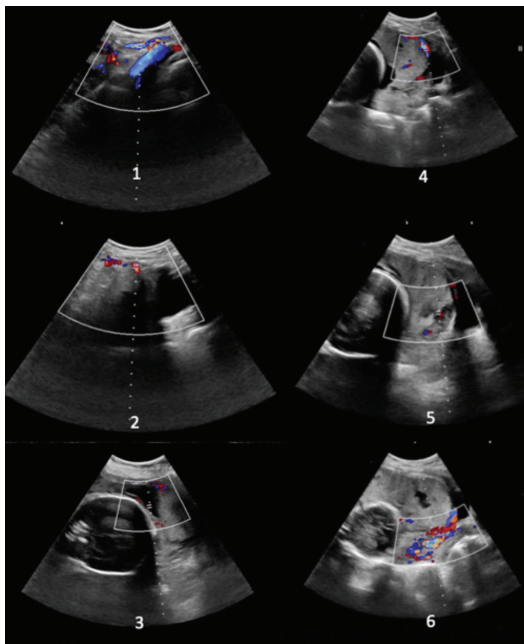


Figure 2. The Doppler sonography in pregnant women with placenta accreta spectrum. (1) The right uterine artery Doppler sonography, (2) The left uterine artery Doppler sonography, (3) The largest lacunae Doppler sonography, (4) The posterior of the bladder Doppler sonography, (5) The posterior lacunae Doppler sonography, (6) Cervix Doppler sonography

Table 3. The Doppler markers and hysterectomy among pregnant women

	Hysterectomy	No hysterectomy	p-value
Number (%)	34 (66.66)	17 (33.33)	
Bladder PSV	46.00 (20, 90)	39.50 (33, 46)	0.005
Cervix PSV	20.00 (0, 76)	20.00 (14, 26)	0.013
The largest lacuna PSV	0.00 (0, 18)	12.5 (0, 25)	0.835
The posterior lacuna of the bladder PSV	0.00 (0, 27)	0.00 (0, 0)	0.373
The left uterine artery PSV	68.00 (61, 135)	82.00 (63, 101)	0.003
The right uterine artery PSV	70.00 (51, 125)	82.50 (77, 88)	0.01
The mean uterine artery PSV	71.50 (59, 110)	82.25 (70, 94)	0.001
The highest PSV	46.00 (20, 90)	39.5 (33.46)	0.008
The left uterine artery PI	0.78 (0.51, 1.75)	1.18 (1.15, 1.22)	0.406
The right uterine artery PI	0.90 (0.54, 76.00)	0.72 (0.69, 0.76)	0.117
The mean PI of the uterine artery	0.89 (0.58, 38.45)	0.95 (0.95, 0.96)	0.374
The left uterine artery RI	0.50 (0.39, 1.00)	0.62 (0.62, 0.63)	0.147
The right uterine artery RI	0.50 (0.40, 0.66)	0.48 (0.47, 0.49)	0.96
The mean RI of the uterine artery	0.51 (0.44, 0.74)	0.55 (0.55, 0.55)	0.374

All data are demonstrated in median (minimum, maximum), PSV: Peak systolic velocity, PI: Pulsatility index, RI: Resistance index

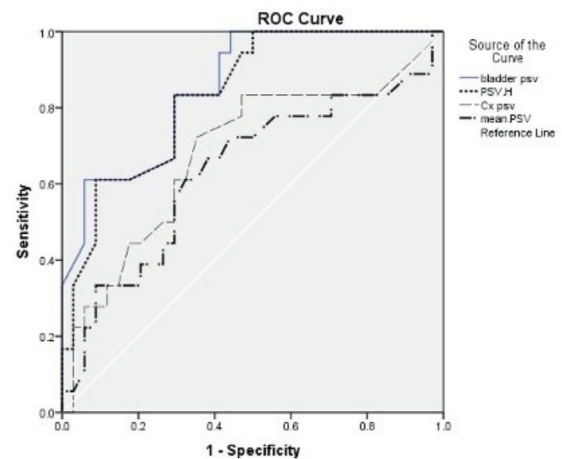


Figure 3. The receiver operating characteristic curve for bladder peak systolic velocity (PSV), cervix PSV, the highest PSV, and the mean PSV for diagnosis of placenta accreta spectrum

ROC: Receiver operating characteristic, PSV: Peak systolic velocity

Table 4. The Doppler markers and histopathology among pregnant women

	PAS 1 (accreta)	PAS 2 (increta and percreta)	p-value
Number (%)	23 (45.09%)	28 (54.91%)	
Bladder PSV	32.00 (20, 64)	46.00 (27, 90)	<0.001
Cervix PSV	18.00 (0, 38)	25.00 (0, 76)	0.053
The largest lacuna PSV	0.00 (0, 41)	0.00 (0, 25)	0.930
The posterior lacuna of the bladder PSV	0.00 (0, 37)	0.00 (0, 31)	0.373
The left uterine artery PSV	68.00 (61, 113)	72.00 (61, 135)	0.049
The right uterine artery PSV	70.00 (60, 125)	77.00 (51, 127)	0.273
The mean uterine artery PSV	71.00 (62, 107)	82.00 (59, 110)	0.111
The highest PSV	32.00 (20, 64)	46.00 (27, 90)	<0.001
The left uterine artery PI	0.77 (0.55, 1.77)	0.81 (0.57, 1.74)	0.220
The right uterine artery PI	0.90 (0.54, 66)	0.82 (0.54, 76)	0.289
Mean PI of the uterine artery	0.88 (0.55, 33.30)	0.91 (0.58, 38.45)	0.912
The left uterine artery RI	0.48 (0.40, 0.74)	0.51 (0.39, 1.00)	0.063
The right uterine artery RI	0.52 (0.40, 0.65)	0.50 (0.40, 0.68)	0.971
The mean RI of the uterine artery	0.50 (0.41, 0.68)	0.52 (0.44, 0.74)	0.153
All data are demonstrated in median (minimum, maximum), PAS: Placenta accreta spectrum, PSV: Peak systolic velocity, PI: Pulsatility index, RI: Resistance index			

Table 5. The diagnostic ability of Doppler ultrasonography by ROC curve

Parameter	Cut-off	AUC*	p	Sensitivity	Specificity
Bladder PSV	41	0.885	<0.001	84%	60%
Cervix PSV	18.5	0.835	<0.001	84%	57%
Highest PSV	38.5	0.681	0.033	84%	60%
Mean PSV	66.7	0.636	0.110	83%	15%
*AUC: area under the curve, ROC: Receiver operating characteristic, PSV: Peak systolic velocity					

Previously, some studies have suggested novel markers derived from Doppler US assessment to evaluate the prognosis of PAS. Al-Khan et al. (16) indicated that the presence of posterior urinary bladder wall pulsatile arterial vessels with low RI could be a suitable marker to predict the severity of the PAS. The present study investigated bladder PSV and showed that

it was associated with severe bleeding, need for post-delivery hysterectomy, and invasive histopathology among pregnant women with PAS.

Yule et al. (17) showed that women confirmed with PAS who needed hysterectomy after the delivery reported an increase in color pixel area near the bladder-uterine serosal interface on transvaginal color Doppler US in the first trimester. The current study was not able to confirm these findings as all subjects were in the third trimester and we used trans-abdominal method. However, we found no significant relationship between the PSV of the posterior lacuna of the bladder and PAS outcomes.

Some studies have investigated the association between placenta accreta invasion and Doppler US findings. Hussein et al. (12) reported that markers described as “numerous coherent vessels involving the serosa-bladder interface” in 2D and 3D Doppler sonography were an independent marker to predict the severity and the complications facing pregnant women with PAS. Firmansha Dilmly et al. (18) showed that the flow index value in 3D Doppler sonography could predict the depth of the invasion in invasive PAS before surgery and the blood loss level. The present study showed that bladder PSV, the highest measured PSV, and the left uterine artery PSV were all significantly associated with invasive forms of PAS (increta and percreta).

In addition, the results of the present study showed that cervical PSV was associated with severe bleeding and a higher rate of hysterectomy among women with PAS. Cervical PSV may be a reasonably sensitive and specific marker to diagnose PAS among women with probable PAS, to enable better clinical decision making for their pregnancy and delivery. Of note in the present study, left uterine artery PSV emerged as a novel marker for diagnosis and predicting prognosis of PAS, which has not been reported previously.

In the present study only one expert prenatal fellow and the same two surgeons for cesarean section and hysterectomy if needed were used. This should minimize differences associated with larger teams of participating clinicians. Emergency deliveries were also excluded, so the blood loss due to the emergency situation was diminished. All pregnant women enrolled in the study were diagnosed with PAS with the appropriate criteria and this was confirmed histopathologically.

Study Limitations

This study has some limitations. The sample size was small and it was a single-center study. The high rate of hysterectomy among the patients was a potential source of bias and resulted from the higher rate of invasive and severe form of PAS among the pregnant women in our study, due to the center being a referral center. Moreover, using transvaginal US in

addition to transabdominal US and evaluating these markers in all trimesters among pregnant women separately could be appropriate in future research.

Conclusion

Bladder PSV, cervix PSV, and mean PSV between uterine arteries were confirmed as novel markers to predict the complications facing women with PAS, such as severe bleeding and hysterectomy. Also, these markers could predict the invasive forms of PAS (increta and percreta). Clinicians and surgeons may consider these markers derived from Doppler US as a non-invasive tool in the third trimester to help manage pregnant women with suspected PAS, with the aim of decreasing the morbidities and mortalities among them. However, further studies with a larger more general population are required to confirm these findings.

Ethics Committee Approval: *This study was approved by the Imam Khomeini Hospital Complex-Tehran University of Medical Sciences Local Ethics Committee (approval number: IR.TUMS.IKHC.REC.1400.201, date: 01.09.2021).*

Informed Consent: *Informed consent was obtained from all participants for inclusion in the study.*

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Investigation of the risk factors associated with osteoporosis in postmenopausal women

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Abstract

Objective: Osteoporosis is a substantial global public health issue. The objective of this study was to evaluate the risk variables associated with osteoporosis among patients seeking care at an outpatient menopausal clinic in a tertiary university hospital.

Material and Methods: In this retrospective, cross-sectional study postmenopausal women who attended the outpatient menopause clinic of Başkent University Hospital between June 01, 2014, and August 31, 2015, were enrolled. Patients' datasheets were reviewed and data including age, body mass index, parity, duration and age of menopause, history of smoking and oral contraceptive pills (OCPs) use, natural or surgical menopause, and calcium-containing food consumption were collected through a standardized questionnaire. Bone mineral density (BMD) was measured at the femur neck and lumbar spine by dual energy X-ray absorptiometry.

Results: A total of 1,148 women with a mean age of 53.5 ± 6.7 years, mean duration of menopause 7.1 ± 6.2 years and mean age of menopause 46.3 ± 5.1 years were identified. Of these, 235 (20.5%) were diagnosed as having osteoporosis. The average femur and lumbar T-values showed a decrease in normal weight patients compared to overweight, obese, and morbidly obese patients ($F=22,337$, $p<0.001$ and $F=50,195$, $p<0.001$, respectively). The mean femur T-values were higher in participants who used OCPs, regularly consumed a calcium-rich diet, and performed regular physical activity ($p<0.05$, $p<0.01$ and $p<0.05$). Positive correlations were noted between giving birth and femur T-values ($r=0.065$, $p=0.027$), between natural menopause and lumbar T-values ($r=0.060$, $p=0.043$), and between consuming a calcium-rich diet and femur T-values ($r=0.087$, $p=0.003$ and $r=0.064$, $p=0.031$, respectively).

Conclusion: Using OCPs, lifelong physical activity, and a healthy diet rich in calcium are important factors for the prevention of low lumbar spine and femoral BMD and by implication, osteoporosis. (J Turk Ger Gynecol Assoc 2023; 24: 235-40)

Keywords: Menopause, osteoporosis, bone mineral density

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Introduction

Menopause is defined as the onset of cessation of ovarian endocrine functions that marks the end of the reproductive years. For most women, menopause occurs between the ages of 45 and 55 as a natural consequence of biological aging due to the loss of follicular function and a decline in estrogen production. As stated by the World Health Organization (WHO), natural menopause is considered to have occurred after 12

months of uninterrupted menstrual cessation without any other apparent physiological or pathological cause or clinical intervention. In some women, "premature menopause" may occur earlier, before the age of 40 years, due to certain chromosomal abnormalities, autoimmune diseases, or other unknown causes. Menopause can also be caused by surgical or medical procedures. In the developed world, with increased life expectancy during the last century, an increasing number



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of women spend more than 20 years in the menopausal period (1,2).

Osteoporosis is among one of the most frequently encountered consequences of estrogen deprivation, substantially impairing the quality of life, and therefore strategies aimed at prevention of bone loss are of importance. Studies indicate that 20% of bone loss may occur during this period and about one in every 10 women is affected by osteoporosis worldwide. Osteoporosis, features of which are very low bone mineral density (BMD) and bone fragility, is characterized by deterioration in the micro- and macro-architecture of the bone tissue. Postmenopausal osteoporosis may frequently lead to bone fractures which are associated with severe pain, reduced mobility, and functional loss (3,4). Among the most widely applied techniques to measure bone density is dual-energy X-ray absorptiometry (DEXA). It is the gold standard technique to diagnose osteopenia and osteoporosis and assessment of the femur neck and lumbar spine are usually recommended by this technique (5).

Osteoporosis is a multifactorial disease in which genetics and environmental conditions play an important role. Like other multifactorial diseases, quantitative phenotype changes occur with the interaction of genotype and environment. It has been well-documented that osteoporosis is affected by environmental factors, such as smoking, diet, physical activity, sunlight, and the use of oral contraceptive pills (OCPs) (6-8). The Food and Drug Administration (FDA) in the USA has authorized a statement regarding the preventative effects of calcium-rich foods on bone health (6,7). The interest in the function of nutrition for the prevention and pathogenesis of osteoporosis is progressing. Recent evidence strongly suggests that while an unhealthy diet results in an increased risk of osteoporosis, a healthy dietary pattern plays a protective role. After all, nutrition is a modifiable factor that plays a role in both building bone mass and preventing osteoporosis. Among the nutrients demonstrated to protect against impaired bone health are calcium, phosphorus, magnesium, and adequate vitamin intake, especially vitamin D. In addition, food that have a positive effect on BMD include milk, dairy products, and red meat rich in fiber and protein (8).

In the bone health report published by the FDA, the importance of physical activity was emphasized at the very beginning. Physical activity and adequately consumed calcium and vitamin D, as part of a well-adjusted diet, may prevent the occurrence of osteoporosis and may build and maintain good bone health (9). Exercise has a substantial effect on BMD and it has been suggested that bone tissue can perceive biomechanical stress by means of an internal "mechanostat" and regulates its remodeling accordingly by increasing bone deposition (10). Mechanical usage (MU) determines bone mass by influencing bone remodeling. Reduced MU decreases new bone formation

and increases bone loss near the bone marrow. Acute and chronic pauses in MU can affect the anatomical and tissue dynamic patterns of the bone, leading to postmenopausal osteoporosis similar to that seen in other forms of osteoporosis. Return to a normal MU stops bone loss through remodeling and enables the available bone to start remodeling increasing protection against osteopenia and osteoporosis (10).

Postmenopausal women are subject to primary osteoporosis as a result of estrogen deprivation. It is recommended that, in addition to physical activity, nutrition and a well-balanced diet are important tools for osteoporosis prevention and ameliorate bone health problems at older ages (8). Likewise, the use of hormone replacement therapy, antiresorptive therapy, and use of calcium-bearing substances during menopause is considered to contribute to a reduction in the risk of osteoporosis (11,12). In the modern world, with increased life expectancy, osteoporosis and osteoporosis-related fractures have become a public health problem that increases mortality and morbidity, especially in menopausal women, placing significant burdens on health resources. The aim of this study was to investigate the osteoporosis-related risk factors in patients who attended the outpatient menopause clinic of the Başkent University Hospital.

Material and Methods

In this cross-sectional, retrospective study, postmenopausal women who attended the Menopause Outpatient Clinic of Başkent University, Training and Research Center, Adana, between June 01, 2014, and August 31, 2015 were enrolled. The datasheets of all patients who were admitted to the outpatient menopause clinic during the study period were screened. Patients with medical disorders that could lead to osteoporosis or fractures, including parathyroid gland or adrenal gland disorders, and those receiving long-term steroids or low molecular weight heparins were excluded. The Başkent University Institutional Review Board provided ethical approval for the present research (approval number: KA22-505, date: 04.01.2023) and the study was conducted according to the principles of the Helsinki Declaration.

All anthropometric measurements of the patients were assessed and recorded. Body mass index (BMI) is calculated by dividing weight in kg by height in meters squared. BMD measurement was done using a Hologic QDR 4500 DEXA scanner device (Hologic, Boston, MA, USA). Measurements included the femoral neck and lumbar spine. According to the WHO criteria, a T-score of ≤ -2.5 was defined as "osteoporosis", a T-score between -1.0 and -2.5 was defined as "osteopenia" and a T-score of > -1.0 was defined as "normal" (5).

Regular physical exercise was defined as doing exercises at least 3 days a week, at least 30 minutes daily. Regular consumption of a calcium-rich diet was defined as 2-4 servings of dairy daily

including 240 mL of milk or yoghurt or 40-60 g of cheese (13). Data regarding the sociodemographic characteristics, lifestyle characteristics, obstetric data and menopause characteristics, medication use, history of fractures and relevant family history of the patients were gathered by a questionnaire prepared by the researchers in the light of the literature.

Statistical analysis

Descriptive statistics, given as mean and standard deviation or frequency and proportions, were calculated to describe the data. Two Independent samples t-test and the Mann-Whitney U test were used for comparisons between paired groups. For comparisons of three or more groups One-Way ANOVA analysis of variance was used, and to determine the difference between the groups a post-hoc Least Significant Difference test was used. Spearman’s correlation analysis was performed to investigate the relationship between various pre-menopausal and menopausal factors that may have an effect on osteoporosis as defined by BMD measurements of the participants. For all tests, $p < 0.05$ was considered significant.

Results

A total of 1,148 menopausal women with a mean age of 53.5 ± 6.7 years (range; 34-82 years), a mean age at menopause of 46.3 ± 5.1 years (range; 26-64 years), and a mean duration of menopause of 7.1 ± 6.2 years (range; 1-35 years) were retrospectively reviewed (Table 1). While 1,017 (88.6%) of the patients were in natural menopause, 131 (11.4%) were in surgical menopause. Of the patients, 193 (16.8%) consumed calcium-rich foods, and 160 (13.9%) performed regular physical activity at least 3 days a week. Thirty (2.6%) of the patients had a history of fracture (osteoporotic fracture/fragility fracture) and 56 (4.9%) had a family history of fracture.

The mean height was 156.9 ± 5.9 cm, the mean body weight was 72.6 ± 12.4 kg, and the mean BMI was 29.4 ± 5.1 kg/m². Based on BMI, 213 (18.6%) were defined as normal weight, 445 (38.8%) were overweight, 454 (39.5%) were obese (39.5%) and 36 (3.1%) were morbidly obese (3.1%). Of the patients, 143 (12.5%) did not use any contraceptive method. Among the patients who used contraception, 899 (78.3%) used non-hormonal methods

such as intrauterine device and condom, and 106 (9.3%) used OCPs. Of the women 1077 (93.8%) were parous and 71 (6.2%) had never been pregnant. The mean gravida was 4.8 ± 2.9 , and the mean number of parity was 3.2 ± 2.0 .

Based on femoral T-values, 52.3% of the patients were in the normal range, whereas 42.8% had osteopenia and 4.9% were found to have osteoporosis. However, for lumbar T-values, 31.4% of the patients were in the normal ranges, while 48.2% were osteopenic and 20.5% were osteoporotic (Table 2). A further comparison of normal, overweight, obese, and morbidly obese women according to obstetric and anthropometric data is presented in Table 3. When women were compared for BMD values according to the contraceptive methods they used, the mean femur T-values were found to be significantly higher among women who had used OCPs ($p=0.040$, and $p=0.035$, respectively) (Table 4). No difference was found in mean lumbar T-values according to OCP use.

In pairwise comparisons according to the type of menopause, compared to the surgical menopause group, the mean lumbar BMD values were significantly higher in the natural menopause group (0.86 ± 0.12 vs. 0.88 ± 0.16 ; $p=0.041$) (Table 5). The mean lumbar T-value was significantly higher in natural menopausal group (-1.45 ± 1.26) than in surgical menopause group (-1.70 ± 1.09), ($t=2.395$, $p=0.018$). The mean femur T-values were significantly higher in those who regularly consumed calcium-rich foods (-0.73 ± 1.07) compared with those who did not consume calcium-rich foods (-0.92 ± 1.0), ($t=-2.359$, $p=0.018$). The mean femur T-values were found to be significantly higher in those who engaged in regular physical activity (0.77 ± 1.14) than in those who did not (0.74 ± 1.13), ($t=-2.496$, $p=0.013$). No statistically significant difference was found between smoking, hormone replacement and antiresorptive therapy, calcium use, and any of the BMD measurements.

Spearman correlation analysis identified several significant correlations, including weak positive correlations between femur T- and gravida and parity ($r=0.065$, $p=0.027$ and $r=0.092$, $p=0.002$, respectively). While a statistically significant positive correlation was demonstrated between natural menopause and lumbar T-values ($r=0.060$, $p=0.043$), a significant positive

Table 1. Anthropometric characteristics of the study population

Variable	Mean ± SD	Range
Age, years	53.5 ± 6.7	34-82
Age at menopause, years	46.3 ± 5.1	26-64
Duration of menopause, years	7.1 ± 6.2	1-35
BMI (kg/m ²)	29.4 ± 5.1	17.2-55.7

SD: Standard deviation, BMI: Body mass index

Table 2. Bone mineral density measurements of the study population and their stratification according to T-values

Area of BMD measurement	Normal, (n, %)	Osteopenia, (n, %)	Osteoporosis, (n, %)
Femur T-value	600 (52.3%)	492 (42.8%)	56 (4.9%)
Lumbar spine T-value	360 (31.4%)	553 (48.2%)	235 (20.5%)

BMD: Bone mineral density

Table 3. Comparison of normal, overweight, obese and morbidly obese women with a reference to anthropometric data

Patient characteristics and BMD measurements	Normal, (n=213), (mean ± SD)	Overweight, (n=445), (mean ± SD)	Obese, (n=454), (mean ± SD)	Morbid obese, (n=36), (mean ± SD)	F	p
Age (years)	51.6±6.5	53.3±6.6	54.3±6.8	56.7±6.5	10,817	<0.001
Gravida (n)	3.6±2.2	4.8±3.0	5.3±2.8	5.8±3.8	18,842	<0.001
Parity (n)	2.2±1.4	3.0±2.0	3.7±2.1	4.1±2.7	28,798	<0.001
Menopause age (years)	44.8±5.2	46.4±4.8	46.9±4.9	47.0±7.0	8,590	<0.001
Duration of menopause (years)	6.7±5.6	6.8±6.1	7.3±6.3	9.7±8.9	2,864	0.036
Femur T-value	-1.379±0.93	-1.055±0.89	-0.560±1.02	-0.046±0.98	50,195	<0.001
Lumbar T-value	-1.755±1.25	-1.607±1.16	-1.282±1.26	-0.849±1.39	12,282	<0.001

BMD: Bone mineral density, SD: Standard deviation, *One-Way ANOVA test

Table 4. Comparison of densitometric measurements according to the contraceptive methods used during the reproductive ages

Area of BMD measurement	No contraceptive method, (n=143)	Non-OCP method, (n=899)	OCP use, (n=106)	F	p
Femur T-value	-0.8821±0.970	-0.9171±1,007	-0.6465±1,133	3,370	0.035[†]
Lumbar T-value	-1.5267±1,277	-1.5062±1,234	-1.2168±1,255	2,681	0.069

BMD: Bone mineral density, OCP: Oral contraceptive pills, [†]One Way ANOVA test, [†]p<0.05

Table 5. The correlations between BMD values and obstetric data, menopause status, medication use, and lifestyle characteristics

Variation	Spearman's rho	Femur T-value	Lumbar T-value
Gravida	r	0.065*	-0.035
	p	0.027	0.231
Parity	r	0.092**	-0.022
	p	0.002	0.456
Natural menopause	r	0.030	0.060*
	p	0.315	0.043
Premature menopause	r	-0.055	-0.042
	p	0.063	0.158
Hormone replacement therapy	r	-0.018	-0.023
	p	0.553	0.430
Antiresorptive therapy	r	-0.019	0.031
	p	0.520	0.295
Calcium preparation	r	0.006	0.029
	p	0.849	0.321
Smoking	r	-0.019	0.009
	p	0.511	0.772
Regular consumption of calcium-rich food	r	0.064*	0.022
	p	0.031	0.455
Practicing regular physical exercise	r	-0.044	0.009
	p	0.138	0.772

BMD: Bone mineral density, r: Spearman's rho. *Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed)

correlation was found between consuming calcium-rich foods regularly and femur T-values (r=0.064, p=0.031). A positive, significant correlation was found between regular physical activity and femur T-values (r=0.076, p=0.010), (Table 5).

Discussion

In this cross-sectional, descriptive study enrolling a total of 1148 postmenopausal women who attended the outpatient menopause clinic of a tertiary university hospital, the mean femur BMD and T-values were higher in those who used OCPs during the pre-menopausal period, those who had natural menopause and those who consumed calcium-rich foods. In addition, the mean femur BMD values were found to be higher in those who were parous and performed regular physical activity.

İpek et al. (14) evaluated osteoporosis risk in 537 postmenopausal women aged 45 years and older. The mean age was 59.5±8.6 years, the mean age at menopause was 49.0±3.4 years and the mean duration of menopause was 13.8±1.4 years. Lumbar T-values showed that 24.0% (n=129) were normal, 44.1% (n=237) were osteopenic and 31.8% (n=171) were osteoporotic. Again, different proportions were found when evaluating femur T-values: 40.2% (n=216) had normal BMD; 48.8% (n=262) were classified as osteopenic; and 11% (n=59) were osteoporotic (14). In the present study, the mean age of the patients was younger, and the mean age at menopause was lower, the duration of menopause was longer, and according to lumbar T-values, the rate of having a normal

BMD (31.4%) and osteopenia (48.2%) were lower, and the rate of osteoporosis (20.5%) was higher as compared to the study of İpek et al. (14).

In studies conducted in postmenopausal women, a significant relationship was shown between BMI and lumbar and femoral BMD values (15-17). According to our results, the mean femoral BMD and lumbar BMD values of the participants were significantly higher in overweight, obese, and morbidly obese women in comparison to those with normal weight. This result suggests that increased body weight can play a protective role against osteoporosis in postmenopausal women. However, in a study by Gürlek et al. (18), increased body weight showed a positive association with BMD, while increased waist circumference had a negative effect on BMD. Researchers have suggested that obesity may increase BMD values with mechanical effects, on the other hand abdominal obesity may dysregulate bone metabolism through systemic inflammation (18).

In a population-based study by Nguyen et al. (19) examining the relationship between lifestyle factors and BMD in the aged population, it was found that BMD was affected by calcium consumption and muscle strength. Femoral neck BMD measurement was about 5% higher in both men and women with higher quadriceps strength and calcium consumption, compared to those with lower muscle strength and lower calcium consumption (19). In the study by Ilesanmi-Oyelere and Kruger (8) investigating the relationship between nutrition and bone health in the postmenopausal period 127 women aged 54-81 years were enrolled. The study revealed a favorable link between the consumption of foods containing high levels of calcium, riboflavin, and phosphorus, and BMD in the lumbar region and femoral neck (8). In the present study, a significant but very weak positive correlation was found between a regular calcium-rich diet and femur BMD. The mean femur T-values were significantly higher in those who consumed calcium-rich foods compared to those not consuming calcium-rich foods.

A meta-analysis has shown evidence of the beneficial effects of exercise, specifically those involving varied impact loading characteristics, on the lumbar spine and femoral neck in elderly individuals (20). It was suggested that exercise can be an effective intervention for promoting bone morphogenesis in patients with osteoporosis (20,21). In the present study, we found mean femoral BMD was significantly higher in those who practiced regular physical activity as opposed to those who did not, and a significant but very weak positive correlation was noted between regular physical activity and femoral BMD.

In a systematic review of 75 studies, the effect of OCP use and hormone replacement therapy on BMD was assessed

in premenopausal and perimenopausal women. A positive effect on BMD was demonstrated in perimenopausal women receiving OCPs (11). Studies have shown that this is particularly related to estrogen, which plays a critical role in bone homeostasis with well-known beneficial effects on bone mass, although the mechanism is not fully understood. In the context microenvironment, estrogen has a crucial role on osteoclastic and osteoblastic functions, preventing tonic bone turnover and sustaining bone formation and resorption balance. In a retrospective cohort study conducted on 110 perimenopausal Korean women older than 40 years, Kim et al. (22) concluded that the decrease in BMD in both the lumbar and femoral regions in the perimenopausal period was associated with active bone turnover, and that OCPs may prevent bone loss by suppressing bone turnover. In the present study, an assessment of the contraceptive methods used during the pre-menopausal period revealed that the mean femoral BMD values were higher in those who used OCPs compared to those who used non-OCP methods. There was a very weak positive correlation between giving birth and femoral T-values. This may be because of the use of regular calcium supplementation throughout the pregnancy as a part of national health policy. A study by Yaraman and Karaoğlan (23) investigating osteoporosis-related risk factors among postmenopausal women and revealed a significant relationship between age, daily calcium intake, menopause age, tea and coffee consumption, BMI, parity, and exercise and lumbar and femoral neck T-scores. Moreover, Schnatz et al. (24) found that multiparity and history of breast-feeding decreased the development of osteoporosis in postmenopausal women.

Study Limitations

Our study has some limitations. We calculated BMI by measuring height and weight, but we did not measure waist circumference. We also suggest that it would be more accurate to evaluate postmenopausal women in terms of osteoporosis risk by measuring waist circumference and calculating homeostasis model assessment of insulin resistance, a measure of insulin resistance, and to assess BMD measurements by considering other criteria of the metabolic syndrome. The strength of our study is the enrollment of a large study sample size. Since it is regional research with a large sample size, it provides useful regional data about osteoporosis. Despite the large sample size, due to being a single-center study, and reflecting the eating and exercising behaviors of a single region, the results cannot be extrapolated to the whole country. Further studies performed in various regions and conducted in a multi-center design would definitely contribute to the results of the current study.

Conclusion

This retrospective, cross-sectional study of a large sample revealed effects of OCP use during the fertile period, lifelong physical activity, and a healthy diet rich in calcium for the prevention of osteoporosis in the postmenopausal period. Given the increasing proportion of the aged population, osteoporosis and osteoporosis-related fractures have not only become an important public health concern, but also hamper the quality of life of the elderly. It is important to be aware of strategies to prevent or alleviate osteoporosis-related long-term consequences.

Ethics Committee Approval: The Başkent University Institutional Review Board provided ethical approval for the present research (approval number: KA22-505, date: 04.01.2023) and the study was conducted according to the principles of the Helsinki Declaration.

Informed Consent: Retrospective study.

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Impact of scoliosis on gestational outcome

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Abstract

Objective: To demonstrate the impact of scoliosis on pregnancy and gestational outcome.

Material and Methods: We retrospectively evaluated gestational outcomes of pregnant women with scoliosis at Hacettepe University Hospital between 2008 and 2018. Cases were grouped according to the presence of previous scoliosis surgery and compared in terms of gestational week at birth, birthweight, rate of neonatal intensive care unit admission, hospitalization during pregnancy, route of delivery, type of anesthesia at labor and postpartum intensive care unit admission rate. Ejection fraction (EF), functional vital capacity (FVC), forced expiratory volume (FEV1) and FEV1/FVC ratio values were also recorded.

Results: A total of 23 women were included, of whom 12 (52.2%) had a prior scoliosis surgery. One of the 23 (4.3%) cases was terminated due to respiratory problems, while the remaining 22 cases resulted in deliveries. The median gestational week at birth was 38.2 and the median birth weight was 3150 g. Median (range) maternal height was 143 (80-160) cm while median (range) maternal weight was 51 (35-86) kg. Three (13.6%) were diagnosed with restrictive lung disease. No significant difference was found between operated and non-operated groups in terms of respiratory function test results, cardiac EF and other related demographic and clinical features. Overall cesarean delivery rate was 63.6% (14/22) and cesarean section rate was significantly higher in the operated group (83.3% versus 40%) ($p=0.04$).

Conclusion: Cesarean section rate was increased in this cohort of pregnancies in women with scoliosis and who had previous scoliosis surgery. (J Turk Ger Gynecol Assoc 2023; 24: 241-5)

Keywords: Pregnancy, scoliosis, respiratory function tests, obstetric outcomes, neonatal outcomes

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Introduction

Scoliosis is a medical condition in which a the spine has a sideways curve due to a range of etiologies resulting in a change of the normal structure (1). Conventionally, a curvature greater than 10° is defined as scoliosis (1). Idiopathic scoliosis is generally divided into two groups according to onset of the disease, as early and late (2). Late onset, which is also defined as adolescent idiopathic scoliosis, comprises 80-85% of cases (3-5).

The etiology of idiopathic scoliosis is not clear. The etiology of vertebral abnormalities may involve a wide range of factors (6). These include environmental and genetic factors, vitamin

deficiency, chemical exposure, medications, abnormalities in growth hormone and melatonin secretion, and impaired connective tissue structure and paraspinal musculature may contribute to the pathogenesis (6-8). A female to male ratio of 3.5:1 was reported and progression of scoliosis was found to be 10 times higher in women than men (9,10). It is known that progression of the curve in scoliosis is associated with growth (11). Therefore, large changes in the degree of scoliosis is not expected in adulthood (12,13). The reported incidence of scoliosis during pregnancy varies from 0.02% to 0.7% (14). Although there are a limited number of studies about pregnancy outcomes of patients with scoliosis, most of the studies did not demonstrate adverse outcomes (14-16).



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However, there are controversial results regarding the effect of pregnancy on the progression of scoliosis. Some studies have suggested that pregnancy causes a progression of scoliosis and some other vertebral changes (17-20). However, many studies have concluded that pregnancy does not lead to increased curvature in scoliosis (16,18,21,22).

The aim of this study was to evaluate the clinical characteristics and gestational outcomes of pregnant women with scoliosis who were followed up at a single center.

Material and Methods

We retrospectively evaluated the gestational outcomes of pregnant women with scoliosis who were followed up at Hacettepe University Hospital between 2008 and 2018. The required data were extracted from the institutional electronic database.

Demographic characteristics and clinical findings of the patients, such as maternal age, gravidity, parity, number of miscarriages, maternal height and maternal weight were recorded. Echocardiography and respiratory function test results during pregnancy were evaluated in eligible cases. Ejection fraction (EF), functional vital capacity (FVC), forced expiratory volume (FEV1) and FEV1/FVC ratio values were recorded. Gestational week at birth, birthweight, rate of neonatal intensive care unit (NICU) admission, hospitalization during pregnancy, route of delivery, type of anesthesia at labor and postpartum intensive care unit (ICU) admission rate were evaluated.

Patients were divided into two groups according to previous scoliosis surgery. EF and respiratory function tests, hospitalization during pregnancy, route of delivery, gestational week at birth, birth weight and NICU admission rate, type of anesthesia and postpartum ICU admission rate were compared between these two groups.

Statistical analysis

Statistical analyses were performed with the Statistical Package for the Social Sciences v22 (IBM Inc., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to evaluate the normal distribution of the data. When the data were not normally distributed, median values together with range were used. Mann-Whitney U test was performed for the comparison of median values amongst the groups. Categorical variables were compared using chi-square test. A $p < 0.05$ was considered statistically significant.

Written informed consent was obtained from all the patients, and the study was approved by the Institutional Ethics Committee of Hacettepe University (approval number: GO 18/1077-33, date: 20.11.2018).

Results

The study included 23 pregnant women who were previously diagnosed with scoliosis. The median (range) age was 26 (20-35) years. Only one out of 23 pregnancies resulted in termination of pregnancy (4.3%), while the remaining 22 cases resulted in live deliveries. Scoliosis was classified as thoracic, thoracolumbar or lumbar in 56%, 22% and 22% of the cases, respectively. Median maternal height was 143 (80-160) cm while median maternal weight was 51 (35-86) kg. All the demographic characteristics and clinical findings of the patients are summarized in Table 1. Twelve of the patients (52.2%) had prior scoliosis surgery. The number of previous surgeries was 1, 3, 4, 6 and 9 for 5, 4, 1, 1 and 1 cases, respectively. Median EF value of the patients was 65 (61-70) %. None of the patients were evaluated as having cardiac insufficiency based on their EF values. Median FVC value was 1.96 (0.84-4.30) L, median FEV1 value was 1.79 (0.55-3.39) L and median FEV1/FVC ratio was 85.8 (65.5-92.2). Three (13.6%) patients were diagnosed as having restrictive lung disease. 8 (36.4%) patients required hospitalization during pregnancy. Hospitalization indications were respiratory problems, preterm labor and preeclampsia for 4, 3 and 1 cases, respectively. No significant correlation was found between the route of delivery and whether the scoliosis was thoracic, thoracolumbar, or lumbar. Cesarean delivery rate was 63.6%. Regional or general anesthesia was used in 4 (28.5%) and 10 (71.5%) cases, respectively. Median duration of hospitalization was 4 (2-40) days. Three mothers (13.6%) were admitted to the ICU in the postpartum period due to pneumonia, restrictive lung disease and pericardial effusion. These patients were observed for two days in the ICU. The median gestational week at birth was 38.2 and the median birth weight was 3150 g. The earliest gestational week at birth was 34, while the lowest birth weight was 1600 g. Three newborns were admitted to the NICU due to prematurity (Table 2).

One pregnancy was terminated at the 22nd week of gestation due to maternal respiratory function problems. The patient's height was 80 cm and weight was 35 kg. According to the results of the respiratory function test performed at the 20th week of gestation, the FVC value was 1.05 L, the FEV1 value

Table 1. Demographic characteristics and clinical findings

	Median (range)
Age, years	26 (20-35)
Gravida	2 (1-3)
Parity	0 (0-2)
Abortions	0 (0-2)
Maternal height (cm)	143 (80-160)
Maternal weight (kg)	51 (35-86)

was 0.55 L and the FEV1/FVC ratio was 80%. In this woman echocardiography reported the EF as 60%, and first-degree mitral insufficiency and tricuspid insufficiency were present. There was no cardiac insufficiency. The patient’s respiratory problems gradually increased and she was hospitalized at the 22nd gestational week. The patient was referred to the departments of chest diseases and cardiology. After consultation with all involved specialities, termination of pregnancy was performed with the patient’s informed consent. Median values for FVC, FEV1, FEV1/FVC, EF, gestational week at birth, birth weight, hospitalization during pregnancy, rates of admission to the NICU, route of delivery, type of anesthesia and postpartum admission to the ICU were comparable between the previous scoliosis surgery and non-surgery groups. There was a significant difference between the two groups in terms of the route of delivery. The rate of cesarean section in the group without previous scoliosis surgery was 40%, while in the group with previous surgical history this rate was 83.3% (p=0.04) (Table 3).

Table 2. Descriptive characteristics, pregnancy outcomes and neonatal outcomes

	Median (range)
Gestational week at birth	38.2 (34.3-40.2)
Birthweight, g	3145 (1,600-4,220)
Route of delivery[†]	
Vaginal delivery [†]	8 (36.4)
Cesarean section [†]	14 (63.6)
Anesthesia[†]	
Regional [†]	4/14 (28.5)
General [†]	10/14 (71.5)
Number of previous scoliosis surgeries	1 (0-9)
Cardiac findings (n=20)	
Ejection fraction, %	65 (61-70)
Rate of cardiac insufficiency [†]	0%
Respiratory findings (n=12)	
FVC	1.96 (0.84-4.30)
FEV1	1.79 (0.55-3.39)
FEV1/FVC (%)	85.8 (65.5-92.2)
Rate of restrictive lung diseases (n=3) [†]	3/22 (13.6)
Admissions to intensive care unit [†]	3/22 (13.6)
Duration of hospitalization	4 (2-40)
Hospitalization during pregnancy [†]	8/22 (36.4)
Respiratory problems	4 (18.2)
Early pregnancy complications	3 (13.6)
Preeclampsia	1 (4.6)
[†] Data shown as n (%) or n/total n (%), FVC: Functional vital capacity, FEV1: Forced expiratory volume	

Discussion

Idiopathic scoliosis is a three-dimensional spine deformity of unknown etiology (10). It has been reported that scoliosis has no adverse effect on pregnancy, and *vice versa* (16,18,21-23). However, some studies have suggested that pregnancy increases scoliosis curvature (17,19,24).

In a study by Lebel et al. (15), scoliosis was found to be significantly associated with labor induction and increased rates of cesarean deliveries, although it was concluded that scoliosis was not a risk factor for adverse pregnancy outcomes and especially birth dystocia, using multiple logistic regression analysis. Our findings are consistent with the literature. In this study, scoliosis was not associated with adverse pregnancy outcomes.

Cesarean delivery rate was 63.6% in our series. Previous studies also reported cesarean section rates as high as 41% (25). Despite a lack of consensus, the high cesarean rate was mostly associated with the fear of the patients, inadequate pelvic capacity of patients and the necessity for timely planning of the delivery. For these reasons, although scoliosis is not an absolute indication of cesarean section, it may be a facilitating factor.

In a study evaluating 27 pregnancies of 17 scoliosis patients conducted in Hong Kong, it has been shown that the

Table 3. Comparison of pregnant women with and without previous history of scoliosis surgery

	Previous scoliosis surgery	No previous scoliosis surgery	p
FVC (L)	2.2	2.16	0.414
FEV1 (L)	1.97	1.88	0.710
FEV1/FVC (%)	85	85	0.604
EF (%)	65	66.5	0.605
Gestational week at birth	38.2	36.2	0.566
Birthweight (g)	2,890	2,860	0.880
Hospitalization during pregnancy [*]	5	7	0.799
Admission to NICU [*]	3	0	0.082
Route of delivery			
Cesarean section [*]	10	4	0.040
Vaginal delivery [*]	2	6	
Type of anesthesia			
Regional [*]	2	2	0.056
General [*]	8	2	
Admission to ICU [*]	3	0	0.082
[*] Number of cases. FVC: Functional vital capacity, FEV1: Forced expiratory volume, EF: Ejection fraction, NICU: Neonatal intensive care unit, ICU: Intensive care unit			

complication rates were similar to the general population (14). In our study, the results were consistent with the general population in terms of pregnancy complications.

In a retrospective study by Chan et al. (16) the rate of obstetric complications including preterm delivery or induced labor were found to be not associated with the severity of scoliosis curve or prior spinal fusion. Furthermore, it was reported that the rate of spinal anesthesia was 70%. In the present study, the rate of caesarean section (63.6%) and general anesthesia (71.5%), which were higher than previously reported. Relevant risk factors, such as anatomic problems and patient anxiety were defined for lower rates of regional anesthesia (26). In a case-matched study, 41 patients who underwent scoliosis surgery were evaluated and it was argued that technical difficulties may be experienced in regional anesthesia (27). Most of the group requiring general anesthesia included patients with lumbar scoliosis and thoracolumbar scoliosis who had a previous history of operation. This rate suggests that spinal anesthesia failure increases in patients with scoliosis surgery and scoliosis involving the lumbar region.

In previous studies, it has been reported that pregnancy may have an effect on back pain of the patients with scoliosis and quality of life after pregnancy despite there being no need for further surgeries related to scoliosis (22,28). Consistent with this, only one of our patients needed orthopedic revision at three years after birth. However, it is not clear whether revision surgery was related to pregnancy.

Study Limitations

The main strengths of this study were the single center design of the study and the relatively high number of parameters evaluated. The main limitations were the retrospective design and the relatively small number of patients. Further limitations include a lack of information on the effect of pregnancy on scoliosis and orthopedic findings.

Conclusion

In this study, pregnant women with scoliosis did not have increased rates of adverse pregnancy outcomes, as previously reported. However, previous scoliosis surgery emerged as a risk factor for cesarean section. Further studies with a larger number of patients are needed to confirm these results.

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Ethics Committee Approval: *The study was approved by the Institutional Ethics Committee of Hacettepe University (approval number: GO 18/1077-33, date: 20.11.2018).*

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Levonorgestrel-releasing intrauterine device to treat abnormal uterine bleeding; not one treatment option fits all

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Abstract

Objective: Initially, medical treatment options are preferred in patients with abnormal uterine bleeding (AUB) who are hemodynamically stable. The aim of the present study was to investigate the effectiveness of a levonorgestrel-releasing intrauterine device (LNG-IUD) in reducing bleeding symptoms in patients with AUB stratified by underlying pathology.

Material and Methods: In line with the polyp, adenomyosis, leiomyoma, malignancy (and hyperplasia), coagulopathy, ovulatory disorders, endometrial, iatrogenic and not otherwise classified classification system, patients who were administered LNG-IUD due to adenomyosis, endometrial hyperplasia, leiomyoma and AUB due to not otherwise classified causes were included in the study.

Results: A total of 172 otherwise patients with a mean age of 42.58 ± 5.00 years were included. The distributions in the adenomyosis, endometrial hyperplasia, leiomyoma and otherwise unclassified groups were 30.8%, 12.8%, 26.2%, and 30.2%, respectively. Overall effectiveness of LNG-IUD in reducing menstrual bleeding was 82%. The proportion whose bleeding decreased was 95.50% in the endometrial hyperplasia group, 88.70% in the adenomyosis group, 55.60% in the leiomyoma group and 92.30% in the not otherwise classified group. The power of the current study was 99%. The efficacy of LNG-IUD was significantly less in the leiomyoma group ($p < 0.05$) and thus this group were more likely to require surgical intervention. The overall incidence of spotting was 50%. Amenorrhea developed in 14% of patients.

Conclusion: While LNG-IUD was more effective in reducing symptoms of AUB in patients with adenomyosis, endometrial hyperplasia and not otherwise classified causes, LNG-IUD was less effective in cases of leiomyoma. (J Turk Ger Gynecol Assoc 2023; 24: 246-51)

Keywords: Abnormal uterine bleeding, adenomyosis, endometrial hyperplasia, leiomyoma, levonorgestrel-releasing intrauterine device

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Introduction

Abnormal uterine bleeding (AUB) is one of the most common complaints for referral to gynaecology outpatient clinics. Approximately one-third of outpatient visits in gynaecology clinics are due to AUB (1). Based on the causes of AUB, the polyp, adenomyosis, leiomyoma, malignancy (and hyperplasia), coagulopathy, ovulatory disorders, endometrial, iatrogenic and not otherwise classified (PALM-COEIN) classification system has been in use since 2011 (2). It is

recommended that all women over the age of 45 years with AUB and women under 45 years with endometrial cancer risk factors should be evaluated with endometrial biopsy (1,3). Heavy menstrual bleeding (HMB) is defined as bleeding that lasts longer than eight days and exceeds 80 mL's during a menstrual cycle. In HMB, the first treatment option in hemodynamically stable patients is medical treatment, and evidence suggests that the most effective treatment method over the long-term is the levonorgestrel-releasing intrauterine device (LNG-IUD) (4-7).



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After placing the LNG-IUD, levonorgestrel is released into the uterine cavity at 20 µg/day (8). Local release of levonorgestrel in the uterine cavity causes leukocyte infiltration, atrophic glandular changes of surface epithelium, and changes in vascularity, with a high rate of decidualization of the stroma in the endometrium. As a result, the secretory activities of the epithelial glands are lost, and the proliferative activities of the endometrium are inhibited. Inhibition of proliferative activity causes thinning of the functional layer of the endometrium. Levonorgestrel also causes atrophic endometrial tissue by reducing epidermal growth factor and insulin-like growth factor as well as preventing the mitogenic activity of estrogen. It is supposed that LNG-IUD is effective in treating endometrial hyperplasia and fibroids through these mechanisms. The LNG-IUD is the first-line treatment option in the treatment of endometrial hyperplasia without atypia (9).

Adenomyosis is a common cause of HMB, infertility and dysmenorrhea in reproductive-aged women. Based on available data, the LNG-IUD is considered the most effective first-line treatment option compared to oral agents (10). The LNG-IUD is effective in reducing bleeding and pain due to adenomyosis by causing atrophy of ectopic adenomyotic foci (11). The aim of the present study was to investigate the effectiveness of LNG-IUDs in reducing bleeding symptoms in patients who attended the gynaecology outpatient clinic with AUB, with patients being grouped according to the underlying pathology of their AUB.

Material and Methods

This retrospective study included patients who were admitted for LNG-IUD follow-up between September 2019 and February 2021. This study complied with the Declaration of Helsinki, and it was approved by the Bursa City Hospital Clinical Research Ethics Committee (approval number: 2021-7/20, date: 21.04.2021). In accordance with the PALM-COEIN classification system, the indications for LNG-IUD placement were: adenomyosis; endometrial hyperplasia; myoma uteri; and HMB due to not otherwise classified causes. Patients who underwent LNG-IUD insertion at our institution or came for follow-up after placement were included. Demographic and clinical characteristics of patients, including age, body mass index (BMI), obstetric history, follow-up periods, endometrial sampling results before LNG-IUD placement and endometrial thickness determined at follow-up after placement were retrieved from the hospital database. Type 0, and 1 leiomyomas, according to the International Federation of Gynecology and Obstetrics classification system, were accepted as exclusion criteria (2). Patients who were given an LNG-IUD for contraception were not included in the study. Patients were diagnosed with adenomyosis in line with the Morphological

Uterus Sonographic Assessment consensus statement by two-dimensional transvaginal ultrasound (12). In patients presenting with AUB, those with endometrial biopsy results of endometrial hyperplasia without atypia or benign pathology were included in the study. Patients who received an LNG-IUD due to persistence of HMB after endometrial polypectomy or endometritis treatment were also included. Since there was no risk factor for endometrial cancer, patients under the age of 45 years who underwent LNG-IUD insertion without endometrial biopsy were also included in the study. The study did not include patients who had LNG-IUD for early-stage endometrial cancer or atypical endometrial hyperplasia. The diagnosis of endometrial hyperplasia was made according to World Health Organization criteria (13). The effectiveness of the treatment was evaluated as an increase in hemoglobin (Hb) values and a decrease in the amount of bleeding reported by the patients during follow-up. The difference in Hb level was calculated by taking the difference between Hb2 and Hb1 levels where Hb1 was the value at the time of admission to the hospital and Hb2 was the Hb value at follow-up after LNG-IUD administration. Patients without a follow-up Hb value were not included in the study. Written informed consent was obtained from all patients.

Statistical analysis

The conformity of continuous variables to normal distribution was examined with the Shapiro-Wilk test, and these variables were expressed as mean \pm standard deviation or median (range) values, as appropriate. Comparison of continuous variables between study groups was performed using the Kruskal-Wallis or ANOVA tests. Subgroup analyzes were performed using the Dunn-Bonferroni test after the Kruskal-Wallis test. Categorical variables were expressed as n (%) and compared between groups using the chi-square and Fisher-Freeman-Halton tests. Subgroup analyses were performed after Bonferroni correction. Statistical analyses were performed using SPSS, version 23.0 (SPSS Inc., Chicago, IL, USA). A p-value of 5% was considered statistically significant.

Post-hoc power analysis was performed on the reported findings of the current study. As a result of the chi-square analysis performed by considering the bleeding reduction rates among the study groups, the effect size measure (w-value) was calculated, and the effect size value was determined as $w=0.41$. Considering the type 1 error of 5% and the total number of patients included in the study was ($n=172$), the power of the current study was determined as 99%. Power analysis calculations were made using G*Power software (14).

Results

A total of 172 patients were included in the study. Demographic and clinical characteristics of the patients are

shown in Table 1. Endometrial sampling was not performed in 24.4% of the patients before the application. The overall effectiveness of LNG-IUD in reducing menstrual bleeding was 82% (Table 2). However, the incidence of spotting was 50% while amenorrhea developed in 14% of patients. Thirteen patients requested removal of the LNG-IUD after placement and thus LNG-IUD tolerability in our study was 92.44%.

Comparing BMI and age by underlying pathology, there was no difference between the groups ($p=0.878$ and $p=0.304$) (Table 2). However, there was a difference between the groups when comparing the pre-placement Hb1 level measurement ($p=0.043$). The median Hb1 measurement was 10.60 in the endometrial hyperplasia group, 11.20 in the adenomyosis group, 10.70 in the leiomyoma group and 11.70 in the not otherwise classified group. In the subgroup analyses in which the groups were compared in pairs, no significant difference was found ($p>0.05$). Percentage changes of Hb2 measurements when compared to Hb1 measurements were calculated [$\Delta\text{Hb}2 \rightarrow \text{Hb}1$ (%)] and these changes did not differ between the groups ($p=0.22$). There was a difference between the groups in the proportions of patients whose bleeding decreased ($p<0.001$) (Table 2). In subgroup analyses, it was found that the leiomyoma group appeared to have the least benefit from LNG-IUD placement in terms of bleeding decrease ($p<0.05$). There was no difference between the groups according to the rate of spotting ($p=0.109$). However, the

duration of LNG-IUD use after placement differed between the groups with the leiomyoma group having the shortest median duration of placement ($p=0.018$). In subgroup analyses, the median duration of LNG-IUD use was significantly longer in the endometrial hyperplasia group than in the leiomyoma group ($p=0.009$). There was no difference between the groups in terms of endometrial thickness at follow-up ($p=0.154$). The incidence of amenorrhea was significantly different between the groups ($p=0.039$) with their being a higher rate of amenorrhea in the endometrial hyperplasia compared to the leiomyoma group (Table 2). In contrast, the rate of amenorrhea did not differ in other subgroup analyses performed between the groups ($p>0.05$). There was a difference between study groups regarding the fall-replacement rate ($p=0.030$). On subgroup analysis, the rate of patients requiring LNG-IUD replacement was higher in the leiomyoma group than in the adenomyosis group ($p<0.05$). The proportion of patients who needed surgical intervention after LNG-IUD placement also differed between the groups ($p=0.001$). On subgroup analyses, patients in the leiomyoma group required surgical intervention more frequently than those in either the adenomyosis and not otherwise classified groups (both; $p<0.05$).

In the endometrial hyperplasia group, follow-up biopsy showed persistent endometrial hyperplasia without atypia in two. Thus, in this group the treatment efficiency of LNG-IUD was 90.91%.

Table 1. Demographic and clinical characteristics of the patients

	(n=172)
Mean age (years)	42.58±5
Median gravida	3 (1-7)
Median parity	2 (1-7)
Indications, n (%)	
Adenomyosis	53 (30.8)
Leiomyoma	45 (26.2)
Endometrial hyperplasia	22 (12.8)
Not otherwise classified	52 (30.2)
Endometrial sampling findings prior to LNG-IUD placement, n (%)	
Proliferative endometrium	44 (25.6)
Secretory endometrium	33 (19.2)
Endometrial hyperplasia without atypia	22 (12.8)
Endometrial polyp + proliferative endometrium	15 (8.7)
Stromal glandular breakdown	12 (7.0)
Superficial endometrium	3 (1.7)
Endometritis	1 (0.6)
Not performed	42 (24.4)
LNG-IUD: Levonorgestrel-releasing intrauterine device	

Discussion

In the present study, the effectiveness of LNG-IUD in reducing menstrual bleeding was investigated in patients with AUB and compared between subgroups based on the underlying pathology. We demonstrated that LNG-IUD was more effective in patients with adenomyosis, endometrial hyperplasia and not otherwise classified groups compared to the leiomyoma group with the decrease in the amount of bleeding ranging from 55.6% in the leiomyoma group to 95.5% in the endometrial hyperplasia group.

In addition to its contraceptive effect, LNG-IUD has been reported to be effective in the treatment of dysmenorrhea, leiomyoma, endometriosis, adenomyosis, and endometrial hyperplasia (15). HMB is a significant cause of anaemia in reproductive-aged women. It has been shown that the LNG-IUD, when used to treatment AUB is effective in increasing Hb values due to both structural and non-structural mechanisms (16). Although an increase in follow-up Hb values was observed in the patient groups in our study, no difference was found between the groups when subgroup analysis based on underlying pathology was performed. It has been reported that LNG-IUD is a treatment option in patients with unexplained HMB, diagnosed with adenomyosis, and the presence of myoma uteri smaller than 3 cm that does not distort the uterine

Table 2. LNG-IUD follow-up findings according to the underlying pathology in abnormal uterine bleeding cases

Total		Endometrial hyperplasia, (n=22)	Adenomyosis, (n=53)	Leiomyoma, (n=45)	Not otherwise classified, (n=52)	p-value
Median BMI (kg/m ²)	28.3 (17.3-41.0)	29.2 (19.0-41.0)	28.3 (21.6-40.9)	28.7 (20.1-39.3)	27.9 (17.3-39.1)	0.878 ^a
Mean age (years)	42.58±5	43.3±6.0	42.45±4.4	43.5±4.4	41.65±5.5	0.304 ^b
Median Hb1 (g/dL)	11.1 (7.5-14.0)	10.6 (8.2-13.0)	11.2 (7.5-13.9)	10.7 (7.5-13.6)	11.7 (7.8-14.0)	0.043^a
Median Hb2 (g/dL)	12.7 (8.0-16.5)	12.6 (10.3-14.4)	13.1 (8.7-16.5)	12.2 (8.0-14.4)	12.95 (9.6-14.8)	-
^a Hb2→Hb1 (%)	+11.41 (-20.8 to +74.4)	+19.5 (-20.8 to +56.8)	+11.1 (-6.62 to +65.3)	+10.18 (-6.6 to +65.3)	+10.09 (-1.59 to +74.4)	0.220 ^a
Decrease in bleeding, n (%)	141 (82)	21 (95.5)	47 (88.7)	25 (55.6)	48 (92.3)	<0.001^c
Spotting, n (%)	86 (50)	8 (36.4)	33 (62.3)	23 (51.1)	22 (42.3)	0.109 ^c
Median LNG-IUD duration in situ (month)	14 (1-60)	24 (6-55)	14 (3-48)	10 (2-48)	13.5 (1-60)	0.018^a
Median endometrial thickness at follow-up (mm)	3 (1-14)	3.25 (1-6)	3 (1-12)	4 (1-14)	3 (1-11)	0.154 ^a
Amenorrhea, n (%)	24 (14)	7 (31.8)	6 (11.3)	3 (6.7)	8 (15.4)	0.039^c
Surgical intervention, n (%)	16 (9.3)	1 (4.5)	3 (5.7)	11 (24.4)	1 (1.9)	0.001^d
Expulsion						
Displacement, n (%)	9 (5.2)	2 (9.1)	0 (0)	6 (13.3)	1 (1.9)	0.030^d
Removal on request, n (%)	13 (7.6)	1 (4.5)	2 (3.8)	4 (8.9)	6 (11.5)	
Spontaneous expulsion, n (%)	4 (2.3)	0 (0)	3 (5.7)	1 (2.2)	0 (0)	
No expulsion, n (%)	146 (84.9)	19 (86.4)	48 (90.6)	34 (75.6)	45 (86.5)	
Data are presented as median (range) or mean ± standard deviation or frequency (%). ^a Hb2→Hb1: Calculated (%) change of Hb2 measurement compared to Hb1 value. BMI: Body mass index, Hb1: Pretreatment hemoglobin value, Hb2: Control hemoglobin value, LNG-IUD: Levonorgestrel-releasing intrauterine device. ^a : Kruskal-Wallis test, ^b : ANOVA test, ^c : Chi-square test, ^d : Fisher-Freeman-Halton test						

cavity (17,18). Patients should be informed that it would be appropriate to wait six months for optimal assessment of treatment efficacy following the LNG-IUD placement (17). Seeru and Anita (19) found that, along with a decrease in the amount of bleeding in 93.3% of the patients, irregular spotting continued for up to six months in some of the patients. In our study population, the effectiveness of LNG-IUD as in terms of decrease in bleeding was 82% overall, with the incidence of spotting at 50%.

Desai (20) evaluated the efficacy of LNG-IUD as a treatment for AUB in 40 perimenopausal patients. In this prospective study, the efficiency of the LNG-IUD in reducing the amount of bleeding was 82.5% at the end of a 12-month follow-up period (20), which is similar to the rate in our cohort. In another prospective study, the efficiency of LNG-IUD on AUB was reported to be 97.5% (21). Wheeler et al. (22) conducted a study to identify alternatives to hysterectomy for AUB showed that LNG-IUD is one of the treatment options, especially in the treatment of AUB due to ovulatory or endometrial causes.

Adenomyosis usually causes AUB in patients aged 40-50 years (23). Most of our study group consisted of patients with adenomyosis. Li et al. (24) evaluated the effectiveness of

LNG-IUD in treating AUB due to adenomyosis. They followed patients for an average of 35 months and observed that with a shortened menstruation period, amenorrhea developed on long term follow-up (24). Song et al. (25) also found that LNG-IUD was effective in the treatment of dysmenorrhea from the first month following its administration, as well as reducing the amount of bleeding associated with adenomyosis. Over a mean follow-up period of 14 months, the frequency of bleeding reduction in our adenomyosis group was 88.70%.

Myoma uteri may be coexistent with HMB, intermenstrual bleeding, or infertility in clinical practice. Patients with fibroids are generally anaemic. In the literature, there are studies supporting the efficacy of LNG-IUD in the treatment of AUB due to myoma uteri (26). LNG-IUD has been shown to be an effective treatment option in AUB, including selected cases with fibroids (27). Banu and Manyonda (28) showed that after LNG-IUD placement in patients with myoma uteri, LNG-IUD has equal efficiency with hysterectomy in increasing the quality of life. Senol et al. (29) evaluated 38 patients with severe menstrual bleeding due to myoma uteri and found that LNG-IUD was an effective treatment method that increased Hb values. Although supportive studies have shown that LNG-IUD reduced

the amount of bleeding due to myoma uteri, two recent reviews reported that the available evidence was not robust enough to recommend LNG-IUD for the treatment of AUB-L (30,31). While spontaneous expulsion rates are around 9.6% for LNG-IUD, this rate rises to 15.8% in the presence of leiomyoma (32). In our study, the group with the lowest continuation of LNG-IUD use was the leiomyoma group with only three quarters continuing to use the LNG-IUD, with an average duration of use of 10 months. In addition, the leiomyoma group was the subgroup with the highest rate of surgical intervention and this group was also the group with the lowest LNG-IUD effectiveness in terms of bleeding reduction.

LNG-IUD is accepted as the first-line treatment option for endometrial hyperplasia without atypia (9,33). In endometrial hyperplasia, 85% to 99% regression has been reported following treatment with LNG-IUD (34). In our study, the efficiency of LNG-IUD was 90.91% in these patients, which is consistent with the literature. Moreover, the biggest decrease in the amount of bleeding was found in the endometrial hyperplasia group. It should be noted that the duration of LNG-IUD use was longest in the endometrial hyperplasia group. In this patient group, in addition to its effect on the reduction of bleeding, highlighting the utility of LNG-IUD for the primary treatment of this underlying pathology, is essential for treatment compliance.

In some patients, the cause of AUB cannot be found. This is the “not otherwise classified” group which constituted 30.2% of our study population. Bleeding decreased in 92.30% of these patients following LNG-IUD administration.

One of the strengths of our study was the finding that LNG-IUD indication should be considered in line with the PALM-COEIN classification in AUB. We believe that our study will be a guide for appropriate patient selection before LNG-IUD administration.

Study Limitations

However, there are many limitations of our study. It was a retrospective study and thus information on the side effect profile associated with LNG-IUD was not available from the hospital database. In addition, the reduction of bleeding was based on patient self-reporting. Another limitation of the study was that Hb2 values were not measured at a fixed time point after LNG-IUD placement.

Conclusion

In the treatment of AUB, LNG-IUD was found to be more effective in patients when the underlying pathology was adenomyosis, endometrial hyperplasia and not otherwise classified groups, but was less effective in cases with leiomyoma. Well-designed randomised controlled trials are required to investigate these findings further and either confirm or refute our findings.

Ethics Committee Approval: *This study complied with the Declaration of Helsinki, and it was approved by the Bursa City Hospital Clinical Research Ethics Committee (approval number: 2021-7/20, date: 21.04.2021).*

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

Peer-review: *Externally peer-reviewed.*

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The surgical and clinicopathological characteristics of primary mucinous ovarian cancer: a single institution 30-year retrospective analysis

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Abstract

Objective: To evaluate the clinicopathological characteristics of primary mucinous ovarian carcinoma (MOC) and define oncologic outcomes.

Material and Methods: This retrospective study reviewed patients diagnosed with primary MOC at a single institution and underwent primary treatment between 1990 and 2019. The clinicopathological factors affecting oncological outcomes and treatment response were evaluated. The Kaplan-Meier method was used to evaluate survival outcomes. Survival curves were compared using the log-rank test.

Results: The cohort's (n=92) median (range) age was 48 (15-82) years. Seventy-five (81.5%) patients were in the International Federation of Gynecology and Obstetrics stage I-II. Forty patients received platinum-based adjuvant chemotherapy. The 5-year progression-free survival was 98% in stage I-II and 17% for stage III-IV (p<0.001). In multivariate analysis, the only independent risk factor for disease failure was stage (hazard ratio: 6.838, 95% confidence interval: 1,358-34,415; p=0.020).

Conclusion: Advanced stage was an independent poor prognostic factor for recurrence in patient with MOC. (J Turk Ger Gynecol Assoc 2023; 24: 252-60)

Keywords: Mucinous ovarian carcinoma, platinum-based chemotherapy, stage, survival, treatment response

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Introduction

Epithelial ovarian carcinoma (EOC) is the most common cause of death among gynecological cancers and it consists of several histologic subtypes, including serous, endometrioid, mucinous, and clear cell, each of which has distinct molecular, genetic, clinicopathological, and oncologic characteristics and outcomes (1-3). Therefore, identifying the histological subtype is critical for the assessment of the prognosis and treatment responses of EOCs (4).

Mucinous ovarian carcinoma (MOC) is a rare histological subtype that accounts for approximately 3% of all EOCs and has distinct clinical, histological and molecular features compared to other histological subtypes; the origin of the MOC has long been controversial (5). MOC has several clinical features that differ from those of the serous ovarian carcinomas (SOC) in terms of age at diagnosis, response to chemotherapy, prognosis, and tumor growth pattern. Although MOC is typically more placid and associated with significantly more favorable clinical outcomes than SOC in its early phases, it has a poorer



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prognosis in its more advanced stages (4-7). Despite these differences, MOC receive similar standard adjuvant therapy to other EOC subtypes. Studies have demonstrated that MOC is less susceptible to conventional chemotherapy in the neoadjuvant, adjuvant, and recurrence settings than the more prevalent high-grade SOCs (5,6,8-13). Due to the rarity and heterogeneity of MOC, adjuvant treatment options, management and risk factors for prognosis remain unclear.

Consequently, the primary objective of this research was to identify the clinicopathologic characteristics, survival rate, and prognosis of MOC, as well as the other related variables. Additional aims were to determine the efficiency of adjuvant platinum-based chemotherapy responses in MOC.

Material and Methods

Patients

This observational study was conducted at a tertiary research hospital. The University of Health Sciences Turkey, Ankara Etilik Zübeyde Hanım Women's Health Training and Research Hospital Research Ethics Committee confirmed that no ethical approval was required (approval number: 90057706-799/May). A retrospective analysis of patients diagnosed with primary MOC and treated at our gynecologic oncology clinic between 1990 and 2019 was conducted. The clinical, surgical, and pathological data of the patients were extracted from the gynecologic oncology department's computerized database system, and the patients' files, pathological reports, and operation notes were all evaluated. Patients with insufficient clinical data or follow-up, synchronized tumors, mixed type tumors or metastatic MOC were excluded from the study.

Pathology

The distinction between primary MOC and metastatic MOC was made according to a combination of clinical and pathological features. Once a diagnosis of MOC had been made, we employed a multidisciplinary approach to differentiate this condition, which was not solely dependent on pathology. To clarify this distinction, preoperative imaging, laboratory results, intraoperative findings (macroscopic features, frozen pathology), postoperative imaging upon suspicion, and endoscopy-colonoscopy, if necessary, were performed. To define the tumors morphology, correlations between macroscopic, microscopic and immunohistochemical features were investigated. Overall, an immunohistochemistry panel containing CK20, CK7, PAX8, ER, SATB2, CDX2, p16, and/or p53 helped the expert pathologists distinguish between primary and metastatic MOC, if needed. Eventually, all findings were correlated, followed by a final decision on primary versus metastatic MOC was made.

Surgery

The International Federation of Gynecology and Obstetrics (FIGO) staging criteria from 2014 were used. Surgical and pathologic evaluations were applied to adapt the FIGO 2014 staging method for use prior to 2014.

In our clinic, standard ovarian carcinoma staging included evaluation of the abdomen, peritoneal cytology, total abdominal hysterectomy, bilateral salpingo-oophorectomy, systematic retroperitoneal lymphadenectomy and omentectomy. Systematic retroperitoneal lymphadenectomy was performed as complete pelvic plus paraaortic lymphadenectomy up to the level of the left renal vein. However, in some cases a lymphadenectomy was not performed according to the decision of the senior surgeon, based on the risk of high co-morbidity or adverse conditions during surgery. In intraoperative observation, if a macroscopic pathology was present, cytoreductive surgery techniques were used to target maximal cytoreduction in addition to staging surgery. Maximal cytoreduction was defined as the absence of visible disease after surgery; optimal cytoreduction was defined as 1 cm of macroscopic residual tumor after surgery; and suboptimal cytoreduction was defined as >1 cm of macroscopic residual tumor after surgery. The fertility-sparing approach was preferred for patients in the reproductive age group who desired fertility. The fertility-sparing method was described as conserving the uterus and at least a portion of at least one ovary. All surgical procedures were conducted by gynecological oncology specialists. The gynecologic oncology tumor council determined the choices for adjuvant treatment based on existing guidelines.

Chemotherapy and clinical response

Patients receiving chemotherapy were evaluated according to RECIST 1.1 criteria for chemotherapy response (14). Clinical response was defined as follows: (1) Complete clinical response, specifically complete disappearance of all target and non-target lesions, and absence of new lesions; (2) partial clinical response defined as at least a 30% decrease in the total size of all the target lesions or the presence of one or more non-target lesions and/or a tumor marker level that stays above the normal range; (3) progressive disease, defined as $\geq 20\%$ increase in the maximum diameter of the target lesion, the appearance of ≥ 1 cm new lesion, or the progression of any non-target lesions; (4) stable disease, defined as lesions that are neither in the partial clinical response group nor in the progressive disease group, based on the smallest sum diameters while under study, as determined at the first-month post-treatment.

The clinical response of the patients was evaluated one month after the initial treatment (surgery + adjuvant therapy). The patients were evaluated using clinical, laboratory parameters

(CA-125 levels), and imaging techniques [magnetic resonance imaging (MRI) or computed tomography (CT)]. Recurrence was defined as the reappearance of disease during the follow-up of patients whose routine examinations had revealed the absence of the condition one month after initial treatment (complete clinical response). The advancement of disease during first-line adjuvant treatment is referred to as “refractory disease”. After initial treatment, refractory disease and recurrence were considered “disease failure”.

Survival

Progression-free survival (PFS) was defined as the amount of time between the initial surgery and the appearance of clinical or radiological signs of disease progression. In addition, PFS was defined as the time between the initial surgery and the final contact with a patient who had no disease-related symptoms. The time between the start of treatment and death from any cause or last contact was determined as overall survival (OS). Patients were checked at three-month, six-month, and annual intervals after surgery. At each follow-up, a gynecological examination, CA125 measurement and abdominal ultrasonography were routinely conducted. Chest X-ray was utilized annually. CT, positron emission tomography-CT and MRI were used when needed.

Statistical analysis

For statistical analysis, SPSS, version 20.0 (SPSS Inc., Chicago, IL, USA) software was used. For continuous data, descriptive statistics were expressed as mean \pm standard deviation or median (minimum-maximum), and for categorical variables, as a number/percentage. Estimates of PFS and OS were determined using the Kaplan-Meier method. Using the log-rank test, survival curves were compared. Using the Cox proportional hazards model, a multivariate analysis was conducted to evaluate independent determinants influencing survival.

Results

Patients' characteristics

There were a total of 121 patients who received a diagnosis of primary MOC. Among these patients, 22 were excluded due to insufficient clinical data or follow-up, six were excluded due to synchronized tumors, and one was excluded because of a mixed-type tumor. The study involved the participation of the remaining 92 patients. The median (range) age was 48 (15-82) years, of which 23 (32%) were younger than 40 years of age. The median tumor size was 20 cm (range; 4-50 cm). Of the patients, 65 (71%) had a grade 1 tumor, 16 (17%) had a grade 2 tumor, and one (1%) had a grade 3 tumor. In total, 89 (96.7%) patients underwent primary cytoreduction, while

three (3.3%) received neoadjuvant chemotherapy. The surgical outcome was identified as maximal, optimal, and suboptimal cytoreduction in 83 (90.2%), 2 (2.2%), and 7 (7.6%) patients, respectively. Seventy-five (81.5%) patients had stage I-II disease, whereas 17 (18.5%) had stage III-IV disease. Only 12 individuals with stage IA and a median age of 22 (15-38) years had fertility-sparing surgery.

Overall, 79 (85.9%) patients underwent a lymphadenectomy and 7 (8.9%) had nodal involvement. The median number of extracted lymph nodes was 35 (2-110). The median preoperative CA-125 level was 71 (2-1476) IU/mL. Ascites was present in 40 (56.5%) patients, and cytology was positive in 16 (17.4%). Omental metastasis was detected in 13 (14.1%). Appendectomy was performed in 77 (83.7%) patients, and appendiceal involvement was observed in 5 (6.5%). Table 1 summarizes the clinical, surgical, and pathological features.

Of the enrolled patients, 40 (43.5%) received postoperative adjuvant therapy. In accordance with current guidelines, in-clinic councils set the adjuvant therapy regimens for all patients. In our cohort, the regimens of adjuvant therapy for all patients were platinum-based therapies, although those included different combinations. Twenty-four (60%) patients received taxane plus platinum, 14 (35%) received cyclophosphamide + fluorouracil + cisplatin and two received other platinum-based chemotherapy regimens. Twenty-three patients receiving adjuvant treatment were in stages I-II, while 17 were in stages III-IV. Twenty-six (65%) patients received six cycles of chemotherapy, 12 (30%) fewer than six cycles and 2 (5%) received nine cycles.

Survival analysis

The median follow-up was 62 (2-140) months. After treatment, a complete clinical response was seen in 29 of 40 (72.5%) who received adjuvant chemotherapy. Refractory disease was observed in 11 (27.5%) patients after adjuvant therapy. In the follow-up, recurrence developed in 5 (17.2%) of 29 patients with complete clinical response to adjuvant chemotherapy. Fifty-two patients who did not receive adjuvant chemotherapy had a full clinical response and no recurrence. In the final analysis, 16 (17%) of 92 patients had disease failure (Figure 1). All patients who underwent fertility-sparing surgery were at stage IA, and none of them received adjuvant chemotherapy. The median follow-up in this group was 96 (24-156) months. Additionally, no recurrence or death was observed during the follow-up period.

Subgroup analysis was also performed for advanced stage (stage III-IV) patients, and it was observed that 82% of these patients had primary cytoreductive surgery and 18% had interval cytoreductive surgery. Of the patients, 47% obtained maximal cytoreduction following surgery. All patients with advanced stages received adjuvant chemotherapy.

Table 1. Patients' characteristics

Characteristics		Mean ± SD	Median (range)	
Age		46±15	48 (15-82)	
Tumor size (cm)		19±8	20 (4-50)	
CA-125 (IU/mL)		112±182	71 (2-1476)	
CA-19-9 (IU/mL)		966±5039	83 (3-33904)	
CEA (IU/mL)		20±15	2.8 (0-300)	
Number of removed lymph nodes		40±28	35 (2-110)	
Number of metastatic lymph nodes		9±9.3	3 (1-24)	
		n	(%)	
FIGO 2014 stage	Stage I-II	75	81.5	
	Stage III-IV	17	18.5	
Outcome of cytoreductive surgery	Suboptimal (residue tumor >1 cm)	7	7.6	
	Optimal (residue tumor ≤1 cm)	2	2.2	
	Maximal (no residue tumor)	83	90.2	
Ascites	Present	40	56.5	
	Absent	52	43.5	
Peritoneal cytology	Positive	16	17.4	
	Negative	70	76.1	
	Not reported	6	6.5	
Grade	1	65	71	
	2	16	17	
	3	1	1	
	Unknown	10	11	
Ovarian tumor laterality	Bilaterally	15	16.3	
	Unilaterally	Left	50	54.3
		Right	25	27.2
	Not reported	2	2.2	
Omental involvement	Present	13	14.1	
	Absent	79	85.9	
Appendiceal involvement ¹	Present	5	6.5	
	Absent	72	93.5	
Peritoneal involvement	Present	11	12	
	Absent	81	88	
Lymphadenectomy	Performed	79	85.9	
	Not performed	13	14.1	
Lymph node metastases ²	Present	7	8.9	
	Absent	72	91.1	
Site of metastatic lymph node	Only pelvic	3	3.3	
	Only para-aortic	1	1.1	
	Pelvic and para-aortic	3	3.3	
Adjuvant therapy	Not received	52	56.5	
	Received	40	43.5	
Chemotherapy regimen	Taxane ³ + platin ⁴	24	60	
	CFP ⁵	14	35	
	Others ⁶	2	5	

Table 1. Continued

Characteristics		Mean ± SD	Median (range)
Clinical response after adjuvant chemotherapy ⁷	Complete clinical response	29	72.5
	Refractory disease	11	27.5
Recurrence ⁸	Negative	76	93.8
	Positive	5	6.2

¹: The 77 patients underwent appendectomy, ²The 79 patients underwent lymphadenectomy, ³Paclitaxel or docetaxel, ⁴Carboplatin or cisplatin, ⁵Cyclophosphamide + fluorouracil + cisplatin, ⁶Platin-based other chemotherapy protocols, ⁷Clinical response after adjuvant chemotherapy in 40 patients received adjuvant chemotherapy was evaluated, ⁸Recurrence was evaluated in 81 patients with complete clinical response. SD: Standard deviation, CA-125: Cancer antigen-125, CEA: Carcinoembryonic antigen, FIGO: International Federation of Gynecology and Obstetrics, CFP: Cyclophosphamide + fluorouracil + cisplatin

After initial treatment (surgery + adjuvant therapy), a complete clinical response could not be obtained in one of the early-stage patients who received chemotherapy. A complete clinical response was achieved in 22 (95.7%) of the 23 patients who received adjuvant chemotherapy in stage I-II, whereas a complete clinical response was obtained in 7 (41.2%) of 17 patients who received adjuvant chemotherapy in stage III-IV ($p < 0.001$). After initial treatment (surgery + adjuvant therapy), the complete clinical response rate of advanced-stage (stage III-IV) patients was 62.5% in those who achieved maximal cytoreduction after surgery and 22.2% in those who had residual disease after surgery. No significant difference was found in terms of overall clinical response between the groups with and without residual disease after surgery in the advanced MOC patients ($p = 0.153$). The characteristics of patients with stages III-IV are given in Table 2.

OS could not be evaluated in the study cohort because the number of deaths ($n = 4$) was insufficient. The five-year PFS percentage for the total cohort was 84%. In univariate analysis, stage (I-II vs. II-IV), tumor size (≥ 20 cm vs. < 20 cm); the presence of ascites, omental metastasis, lymph node metastasis and outcome of cytoreductive surgery (maximal vs. optimal and suboptimal) were significant for PFS (Table 3). In addition, 5-year PFS was 100% in those not receiving adjuvant therapy and 63% in those who received adjuvant therapy ($p < 0.001$). However, all patients who did not receive adjuvant therapy were stage IA patients.

The correlation test was applied to the factors that the univariate analysis had identified as significant. Since lymph node and omental involvement were substantially connected with the stage, they were omitted from the multivariate analysis despite their significance in the univariate analysis. The multivariate analysis model included stage, presence of ascites, tumor size and outcome of cytoreductive surgery (Table 3). In this model, stage was revealed as an independent risk factor for recurrence. Disease failure was approximately 7 times higher in stages III-IV (hazard ratio: 6,838, 95% confidence interval: 1,358-34,415; $p = 0.020$). The estimated 5-year PFS for stages I-II was 98%, however, it was 17% for stages III-IV ($p < 0.001$) (Figure 2).

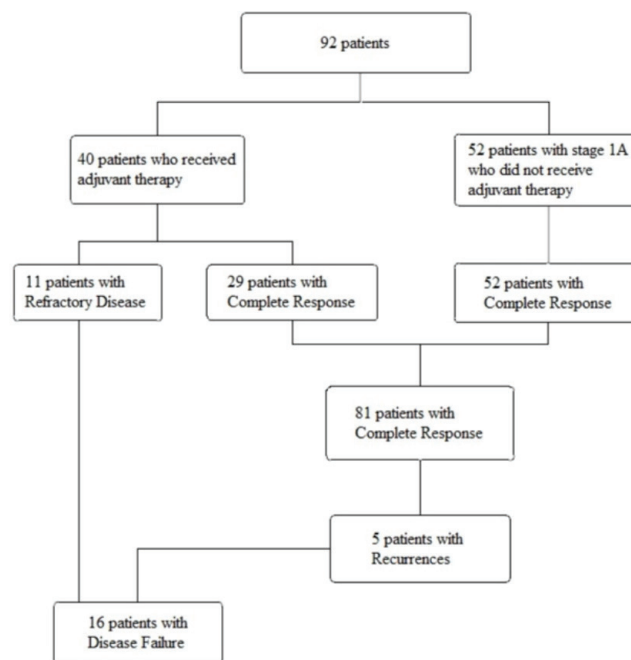


Figure 1. Flow chart of the treatment response of the patients

Table 2. The characteristics of patients with stage III-IV (n=17)

Characteristics		n	%
Outcomes of cytoreductive surgery	Suboptimal (residue tumor > 1 cm)	7	41.1
	Optimal (residue tumor ≤ 1 cm)	2	11.7
	Maximal (no residue tumor)	8	47.2
Chemotherapy regimens	Taxane ¹ + platin ²	13	76.6
	CFP ³	2	11.7
	Others ⁴	2	11.7
Treatment response	Refractory disease	10	58.8
	Complete response	7	41.2
Recurrences	Negative	14	82.3
	Positive	3	17.7

¹: Paclitaxel or docetaxel, ²: Carboplatin or cisplatin, ³: Cyclophosphamide + fluorouracil + cisplatin, ⁴: Platin-based other chemotherapy protocols, CFP: Cyclophosphamide + fluorouracil + cisplatin

Table 3. Factors predicting the progression-free survival

Factors	Univariate analysis		Multivariate analysis			
	5-year progression-free survival		Risk of failure			
		Percentage	p-value	Hazard ratio	95% CI	p-value
Age ¹	≤48 years	88	0.212			
	>48 years	85				
FIGO 2014 stage	I-II	98	<0.001	1 (reference)	1.358-34.415	0.020
	III-IV	17		6.838		
Preoperative CA-125 level	≤35 IU/mL	88	0.065			
	>35 IU/mL	77				
Ascites	Absent	93	0.001	1 (reference)	0.231-18.733	0.514
	Present	72		2.080		
Ascites volume ¹	≤225 cc	73	0.998			
	>225 cc	70				
Tumor size ¹	≤20 cm	75	0.002	1 (reference)	0.000-2.202E105	0.917
	>20 cm	100		Not calculated ⁵		
Lymph node dissection	Do not underwent	69	0.095			
	Underwent	86				
Lymph node metastasis	Negative	91	<0.001			
	Positive	0				
Number of removed lymph node ¹	≤35	86	0.879			
	>35	86				
Omental metastasis	Negative	95	<0.001			
	Positive	15				
Outcome of cytoreductive surgery	Maximal	91	<0.001	1 (reference)	0.322-4.115	0.829
	Suboptimal and optimal	22		1.150		
Fertility sparing surgery	No	82	0.089			
	Yes	100				
Adjuvant chemotherapy combination	Taxane ² + platin ³	52	0.566			
	CFP ⁴	79				

¹Median value, ²: Paclitaxel or dosetaxel, ³: Carboplatin or cisplatin, ⁴: Cyclophosphamide + fluorouracil + cisplatin, ⁵: No event in patients with tumor size more than 20 cm, CI: Confidence interval, FIGO: International Federation of Gynecology and Obstetrics, CA-125: Cancer antigen-125, CFP: Cyclophosphamide + fluorouracil + cisplatin

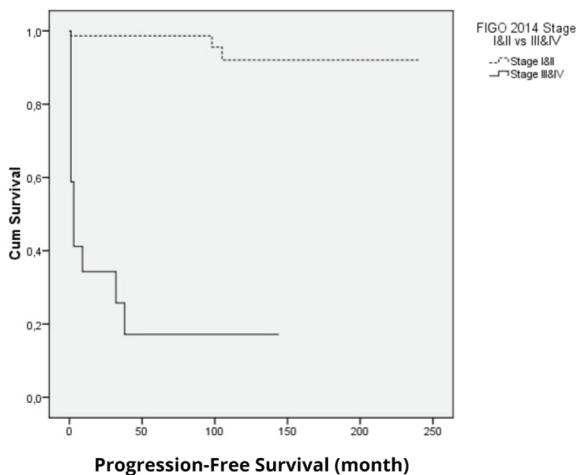


Figure 2. Relationship between progression-free survival and stage
FIGO: International Federation of Gynecology and Obstetrics

Discussion

Clinicopathologic characteristics that may influence the oncologic outcome in MOC were investigated. We observed that advanced FIGO stage was an independent risk factor for PFS. Complete clinical response was not associated with residual disease and was more prevalent in the early stages than in the advanced stages.

MOC is an uncommon histologic subtype of EOC and has different epidemiological, clinical, and molecular features, distinct from other EOCs (5). With advances in histopathological methods and innovations in tumor biology and genetics, the incidence of true primary MOC has declined over the years (6). MOC is generally a unilateral, large ovarian tumor, and more likely to emerge at a younger age, mostly between 36-50 years of age (15). In the current study, 32% of the patients were

younger than 40 years and most of the tumors were unilateral. In contrast to SOCs, MOCs are more often diagnosed at an early stage, which is characterized by a better prognosis for survival. However, at advanced stages, the prognosis is worse compared to other subtypes. It has been found that the mucinous type is a separate risk factor for a poor prognosis in advanced stages (5-8,16-18). In our study, most of the patients were at stage I-II (57% of them at stage IA) and had a better PFS and complete clinical response rate after chemotherapy than stage III-IV. During the follow-up period, no recurrence was observed among 12 patients with stage IA who had undergone fertility-preserving surgery. Young cancer patients in an early stage who desire fertility may be candidates for fertility-preserving surgery (5,6,19).

In the current study, the univariate analysis found that FIGO stage and maximal cytoreduction were identified as the prognostic factors for PFS. In the multivariate analysis, however, FIGO stage was the sole independent prognostic factor for PFS and disease failure was approximately 7 times higher for stages III-IV. Similar results were reported in an earlier study that investigate risk factors for recurrence, where stage and maximal cytoreduction were identified as prognostic factors for PFS in univariate analysis, while in multivariate analysis only stage was associated with PFS (20). In our study, five-year PFS was found to be 84% in the entire cohort, which is consistent with previous reports (17,20,21). We report a 5-year PFS of 17% in stages III-IV similar to the study by Mueller et al. (17).

As with other EOCs, surgical cytoreduction and removing all macroscopic disease are essential for the management of MOCs and survival is associated with the outcome of primary cytoreductive surgery (12,13,22-24). Other studies have reported OS and event-free survival to be significantly affected by residual disease and optimal cytoreduction for advanced MOC to be an important prognostic factor for survival (12,22,24). In our study, univariate analysis revealed that the 5-year PFS for maximal cytoreduction and suboptimal and optimal group was 91% and 22% ($p < 0.001$), respectively, and for the stage I-II, and stage III-IV group it was 98% and 17% ($p < 0.001$), respectively. However, multivariate analysis demonstrated that only stage was independently associated with PFS. Similar results were reported by Hollis et al. (20). However, Simons et al. (25) observed that optimal/complete debulking as opposed to suboptimal debulking did not increase OS in advanced-stage MOC. This was attributed to the presence of metastases in advanced-stage MOC (25).

Several publications have highlighted the resistance of this subtype to conventional chemotherapy (9-12). Hess et al. (9) reported the response rate to standard chemotherapy to be 26% in advanced stage MOC and 65% in serous ovarian cancer. Furthermore, Pectasides et al. (10), Pisano et al.

(11) and Karabuk et al. (12) found the response rates to platinum-based chemotherapy to be 38.5%, 42%, and 57.9%, respectively, in stages III-IV. In the current study, the response rate in patients who received adjuvant chemotherapy at stages 3 and 4 was 41.2%. All these findings imply that advanced stages are associated with poor prognosis and has a restricted chemotherapy response to standard regimens as utilized in SOCs.

Previous research demonstrated that cytoreduction improves the efficacy of chemotherapy by implying that ovarian cancer cells are intrinsically receptive to chemotherapy, thereby increasing patient survival (23,26). Although complete cytoreduction is associated with enhanced survival in women with ovarian cancer histologic subtypes that have a poor response to chemotherapy, it cannot prevent the development of chemotherapy resistance in cells that are already resistant (23). These results indicate that the relationship between cytoreduction and survival may be mediated by a mechanism distinct from chemoresistance. In our study, although maximal cytoreduction was achieved in 47% of patients in stages III-IV, we found that the presence of residual disease at advanced disease was not associated with a higher chemotherapy complete response rate ($p = 0.153$). Although there was no statistically significant difference, there was a clinically significant difference (62.5% vs. 22.2%). The absence of a statistically significant difference may be due to the limited number of patients in this group. Low sensitivity to chemotherapy affects the prognosis overall, and patients with advanced-stage MOC derive less benefit from treatment therapies (5,6).

Although MOCs have different tumorigenic, clinical, and molecular characteristics than SOCs, many physicians continue to use the same treatment strategy and criteria as SOCs because there is no clear consensus regarding the optimal treatment regimen for patients with MOC. Current guidelines for gynecologic (carboplatin and paclitaxel) and gastrointestinal (oxaliplatin, 5-fluorouracil) chemotherapy protocols are acceptable options (19). Although the GOG 241 study ended with a small number of patients, no difference was found in PFS between the two regimens (27). In our cohort, all patients received platinum-based regimens. Therefore, we were unable to make comparisons between regimens. With the improvements in genomic and molecular understanding of MOC, histology based targeted therapies could improve oncologic outcomes.

Study Limitations

The main limitations of this study were its retrospective design and that it covers a wide period between 1990 and 2019, so it includes heterogeneities in the adjuvant therapy regimens. Furthermore, there is a lack of central pathology review.

However extensive study periods are required to collect these rare tumors. In addition, the current study has a large cohort for a single center and has provided sufficient information regarding the oncological outcome and treatment response of patients in early and advanced stages.

Conclusion

In conclusion, stage is the most important factor in determining the prognosis in terms of PFS. The presence of an advanced stage was associated with a poor prognosis and a diminished response to chemotherapy. Residual disease was also a risk factor for disease progression, but it had no effect on chemotherapy response rates in the advanced stages. New molecular and genetic markers should be identified and used to personalize the histology-based treatment for MOC, and additional prospective multicenter trials should be developed for the treatment of advanced stages.

Ethics Committee Approval: *The University of Health Sciences Turkey, Ankara Etlik Zübeyde Hanım Women's Health Training and Research Hospital Research Ethics Committee has confirmed that no ethical approval is required (approval number: 90057706-799/May).*

Informed Consent: *Retrospective study.*

Peer-review: *Externally peer-reviewed.*

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Predictors of recurrence and survival in lymphovascular space invasion negative early-stage endometrioid endometrial cancer patients

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Abstract

Objective: The purpose of this study was to assess prognostic factors correlated with recurrence and decreased oncologic outcomes, as well as the role of adjuvant treatment on survival in women with stage I and II endometrioid endometrial cancer without lymphovascular space invasion (LVSI).

Material and Methods: Patients with LVSI negative, early-stage endometrioid endometrial cancer patients were retrospectively reviewed. Multivariable logistic regression models were used for identifying predictors of recurrence. Overall survival (OS) and disease-free survival (DFS) were estimated using the Kaplan-Meier method, and survival curves were compared by log-rank test. Univariable and multivariable analyses were performed to establish factors affecting OS and DFS. Hazard ratios with 95% confidence intervals were calculated.

Results: A total of 289 patients were included, with a mean age of 58 years and the median surveillance time of 45 (6-147) months. The majority of the patients (54%) had grade 1 tumors. Adjuvant therapy was administered to 68 (23.5%). A total of 13 (4.5%) recurred with median time to recurrence of 52 months. Patients receiving adjuvant treatment were more likely to recur ($p=0.015$), and grade was the only independent predictor of recurrence ($p=0.029$). Five-year OS and DFS were 95.8% and 97.9%, respectively. While tumor size ($p=0.018$) and grade 3 histology ($p=0.045$) were related with shorter DFS, age ($p<0.001$) was the only related factor for decreased OS.

Conclusion: Recurrence rate was low among LVSI negative, early-stage endometrioid endometrial cancer patients. Although recurrences were seen more frequently in patients who received adjuvant treatment, it wasn't an independent prognostic factor. Neither recurrence nor adverse uterine risk factors were associated with shorter OS. While age was the only prognostic factor for decreased OS, grade 3 histology and tumor size were associated with decreased DFS. (J Turk Ger Gynecol Assoc 2023; 24: 261-70)

Keywords: Endometrial cancer, recurrence, lymphovascular space invasion, survival

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Introduction

Cancer of the endometrium is usually diagnosed in the early stages when the disease is limited to uterus and the prognosis is generally good (1,2). Although 5-year overall survival (OS) has been reported as more than 90%, the recurrence rate has been reported as being as high as 30% for the early-stage patients (3,4). Grade, histologic subtype, deep myometrial invasion (MI), lymphovascular space invasion (LVSI), tumor size and age were all found as risk factors for recurrence in stage I and II endometrial cancer (5-7). Based on these risk factors, patients

are classified as low, intermediate, high-intermediate and high risk, and adjuvant therapy is recommended for certain risk groups to lower the recurrence rates (8,9).

LVSI has been of particular research interest in the last decade and has been established as an independent risk factor for recurrence, even when there are no metastatic lymph nodes (10-12). Thus, LVSI has been incorporated into the guidelines as an important prognostic factor, and adjuvant vaginal brachytherapy (BRT) is recommended to LVSI positive patients (9,13).



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However, Neal et al. (14) reported that LVSI was not a prognostic factor in patients with negative nodes after adjusting other prognostic factors. In another study, it was suggested that irrespective of histologic subtype, patients without LVSI and nodal metastasis should be regarded as very low risk of recurrence (15).

Although survival rate is high, and no adjuvant treatment is recommended, recurrences can still be seen in LVSI negative, early-stage patients. Hence, to investigate the effect of LVSI, we planned this retrospective study to identify factors associated with recurrence and the role of adjuvant treatment on outcomes in stage I and II endometrioid endometrial cancer patients without LVSI.

Material and Methods

After the approval of the Ankara University Faculty of Medicine Institutional Review Board (approval number: 10-420-14, date: 09.06.2014), records of 660 women diagnosed with endometrial adenocarcinoma who were treated with surgery at a university hospital from January 2006 till October 2021 were retrospectively reviewed. Four hundred seven patients had tumors without LVSI. Of these patients, 20 were excluded due to non-endometrioid histology, 18 due to stage III/IV disease according to final pathology report and 74 due to missing follow-up data or less than six months of clinical follow-up. A further six patients were also excluded from the analysis because they died of intercurrent diseases in the first six months after surgery. Thus, 289 women with stage I and II endometrioid endometrial cancer without LVSI were included to the final analysis. A written informed consent was obtained from all the patients in order to use their medical data for scientific purposes.

All patients underwent a total hysterectomy ± salpingo-oophorectomy, via open, vaginal or minimally invasive (laparoscopically or robotic assisted) approaches. Four patients, aged between 34 and 40 years had bilateral salpingectomy and the rest had salpingo-oophorectomy. Surgical route was chosen based on surgeon's experience as well as patients' age, weight and co-morbidities. Lymphadenectomy was not performed in 39 patients due to low-risk uterine factors according to Mayo criteria (grade 1-2 endometrioid tumors, <2 cm and <1/2 MI) in frozen section analysis and/or medical comorbidities. In the rest of the patients, lymph node evaluation was performed by sentinel lymph node (SLN) removal only (n=18), SLN mapping followed by pelvic ± paraaortic lymphadenectomy (n=71) or pelvic ± paraaortic lymphadenectomy (n=161). The extent of paraaortic lymphadenectomy varied from removal of suspicious nodes only to systematic lymphadenectomy up to the level of left renal vein, since management practices changed over the

duration of the study period. Peritoneal washings were obtained from all patients who underwent surgery before 2009, but it was not a routine part of the surgery thereafter. Gynecologic oncologists performed all of the surgeries and all specimens were reviewed by experienced gynecologic pathologists.

Following surgery, based on the adverse uterine risk factors (age, grade, deep MI and cervical stromal invasion), patients were either observed or received radiotherapy (RT). Adjuvant RT comprised of BRT and/or external beam radiotherapy (EBRT).

Patients were followed up every three months in the first two years, every six months in the subsequent three years and then annually. Physical and vaginal examination, as well as transvaginal ultrasonography, were performed in each follow-up visit. Computed tomography, magnetic resonance imaging or positron emission tomography were performed only if a recurrence was suspected. Site of recurrences were classified as locoregional, intraabdominal, retroperitoneal and distant.

The demographic data included age, body mass index [(BMI), kg/m²] and menopausal status of the patients. Histopathological data included depth of MI, grade, tumor size and cervical stromal invasion. Clinical and surgical data consisted of CA-125 levels, date of surgery, route of surgery, lymphadenectomy status (yes/no), type of lymphadenectomy, adjuvant treatment (yes/no), type of adjuvant treatment, recurrence (yes/no), recurrence site, recurrence time, last follow-up time and survival.

Disease-free survival (DFS) was defined as time from the surgery until the date of recurrence, or to the date of last contact or death in patients without a recurrence. OS was defined as the time from the surgery until the date of the last follow-up or death.

Statistical analysis

After performing Kolmogorov-Smirnov test to assess normality for continuous variables, data were expressed as median (range) or mean ± standard deviation accordingly and compared using Mann-Whitney U test for non-parametric distributions and Student's t-test for normal distributions. Categorical variables were presented as number (percentage) and compared using chi-square or Fisher's exact tests. Statistically significant factors were assessed with multivariate analysis. By using the Kaplan-Meier method, OS and DFS rates were calculated and the log-rank test was used to calculate statistical significance between the groups. Cox multivariate analysis was used to determine prognostic factors for DFS. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated. SPSS version 23.0 (IBM Corp, Armonk, NY, USA) was used for statistical calculations and a p-value less than 0.05 was considered significant.

Results

The mean age of the 289 patients meeting the inclusion criteria was 58 ± 10.4 years, and ranged from 32 to 86 years. Mean BMI was 33.6 ± 7.4 kg/m². Demographic, clinicopathologic and treatment characteristics of the patients are presented in Table 1. The majority of cases had grade 1 tumors (n=156, 54%) and had $\leq 1/2$ MI (n=231, 80.9%). While 227 (78.5%) had stage IA disease, 54 (18.7%) had stage IB and 8 (2.8%) had stage II disease. One hundred and eighty-five patients (64%) were operated via laparotomy, 101 (34.9%) via a minimally invasive approach and 3 (1%) vaginally. Lymphadenectomy was omitted in 39 (13.5%) patients. Of those undergoing lymph node evaluation, median number of pelvic, paraaortic and SLNs removed were 18 (1-74), 9 (1-41) and 4 (1-20), respectively. A total of 68 (23.5%) patients received adjuvant therapy, including BRT (n=42), EBRT (n=22) and EBRT + BRT (n=4).

The median follow-up time was 45 (6-147) months. A total of 13 (4.5%) patients recurred. Median time to recurrence was 52 (5-138) months. As shown in Table 2, 5 (38.5%) patients had distant, 4 (30.8%) had vaginal vault, 2 (15.4%) had intraperitoneal, in 1 patient there were both distant and nodal, and in a further 1 patient there was both distant and vaginal vault recurrence. Recurrences were managed by surgery (n=1), RT (n=3), chemotherapy (CT) (n=3) or surgery + CT (n=5), and 1 patient refused treatment. While two of these patients died of disease, seven are alive without disease and four are alive with disease. Both patients who died of disease had distant metastases.

Univariate analysis revealed that tumor size (p=0.034), grade (p=0.004), depth of MI (p=0.006), cervical stromal invasion (p=0.045), stage (p=0.002) and adjuvant treatment (p=0.015) were significantly different between the patients with and without recurrence. These significant factors, except for stage (since it did not match the goodness of fit model and is directly associated with depth of MI and cervical stromal invasion) were entered into the multivariate analysis. In multivariate analysis, only grade remained as a significant predictor of recurrence (p=0.029) (Table 3).

Five-year DFS was 97.9%. Cox univariate and multivariate analysis of DFS are presented in Table 4. Age (p=0.005), grade 3 histology (p=0.002), tumor size (p=0.002), deep MI (p=0.002), cervical stromal invasion (p=0.005), stage (p=0.020 for IB and p=0.001 for II) and receiving adjuvant treatment (p=0.008) were related with shorter DFS in univariate analysis. Stage was not entered to the multivariate analysis due to the reasons given above. Only tumor size (HR: 1.07, 95% CI: 1.01-1.13, p=0.018) and grade 3 histology (HR: 12.94, 95% CI: 1.06-157.84, p=0.045) were associated with shorter DFS in the multivariate model (Figure 1a, 2a).

Table 1. Clinicopathological, demographic and treatment characteristics of the patients

Age, years, mean (SD)	58 (± 10.4)
BMI, kg/m ² , mean (SD)	33.6 (± 7.4)
CA-125, median (range)	12.8 (1.2-460.3)
Menopausal status, n (%)	
Postmenopausal	215 (74.4)
Premenopausal	74 (25.6)
Surgical route, n (%)	
Laparotomy	185 (64)
Laparoscopy	94 (32.5)
Robotic	7 (2.4)
Vaginal	3 (1)
Tumor size, n (%)	
≤ 2 cm	116 (40.1)
> 2 cm	173 (59.9)
Tumor size, mm, median (range)	25 (2-100)
Grade, n (%)	
1	156 (54)
2	114 (34.9)
3	19 (6.6)
MI, n (%)	
None	50 (17.3)
$\leq 1/2$	181 (62.6)
$> 1/2$	58 (20.1)
Cervical stromal invasion, n (%)	
Absent	281 (97.2)
Present	8 (2.8)
Stage, n (%)	
IA	227 (78.5)
IB	54 (18.7)
II	8 (2.8)
Lymphadenectomy, n (%)	
Omitted	39 (13.5)
Only SLND	18 (6.2)
BPLND	112 (38.8)
BPPALND	120 (41.5)
Cytology	
Negative	136 (99.3)
Positive	1 (0.7)
Adjuvant therapy	
No	221 (76.5)
BRT	42 (14.5)
EBRT	22 (7.6)
EBRT + BRT	4 (1.3)
Recurrence, n (%)	13 (4.5)

SD: Standard deviation, BMI: Body mass index, CA-125: Cancer antigen-125, MI: Myometrial invasion, SLND: Sentinel lymph node dissection, BPLND: Bilateral pelvic lymph node dissection, BPPALND: bilateral pelvic and paraaortic lymph node dissection, BRT: Brachytherapy, EBRT: External beam radiotherapy

Table 2. Characteristics of the patients with recurrence

Patient	Stage	Type	Grade	Depth of MI	Tm size, mm	Adjuvant therapy	Time to recurrence, months	Site of recurrence	Vital status
#1	IA	Endometrioid	1	≤1/2	20	No	138	Vaginal vault + distant	Alive with disease
#2	IA	Endometrioid	2	≤1/2	30	No	76	Distant + nodal	Alive with disease
#3	II	Endometrioid	3	>1/2	50	EBRT	24	Distant	Died of disease
#4	II	Endometrioid	2	>1/2	55	EBRT	5	Distant	Alive with disease
#5	IA	Endometrioid	3	≤1/2	45	BRT	20	Distant	Alive with disease
#6	IA	Endometrioid	2	≤1/2	20	No	81	Distant	Died of disease
#7	IB	Endometrioid	1	>1/2	50	No	76	Distant	Alive with NED
#8	IA	Endometrioid	2	≤1/2	30	No	47	Intraperitoneal	Alive with NED
#9	IA	Endometrioid	2	≤1/2	35	No	52	Intraperitoneal	Alive with NED
#10	IB	Endometrioid	2	>1/2	40	EBRT	15	Vaginal vault	Alive with NED
#11	IB	Endometrioid	2	>1/2	18	BRT	85	Vaginal vault	Alive with NED
#12	IB	Endometrioid	2	>1/2	20	BRT	82	Vaginal vault	Alive with NED
#13	IB	Endometrioid	3	>1/2	25	BRT	10	Vaginal vault	Alive with NED

EBRT: External beam radiotherapy, BRT: Brachytherapy, NED: No evidence of disease

Table 3. Predictors of recurrence

Patients, n (%)	No recurrence, (n=276) (95.5)	Recurrence, (n=13) (4.5)	Univariate	Multivariate		
			p-value	OR	95% CI	p-value
Age, years, median (range)	57 (32-86)	58 (50-80)	0.144			
BMI, kg/m ² , median (range)	33.2 (18.6-58.7)	28.5 (20.5-43)	0.337			
CA-125, median (range)	12.6 (1.2-460.3)	16.8 (11.1-54.2)	0.929			
Menopausal status, n (%)			1.000			
Premenopausal	71 (25.7)	3 (23.1)				
Postmenopausal	205 (74.3)	10 (76.9)				
Tumor size, n (%)			0.516			
≤2 cm	112 (40.6)	4 (33.3)				
>2 cm	164 (59.4)	9 (66.7)				
Tumor size, mm, median (range)	25 (2-100)	30 (18-55)	0.034	1.01	0.97-1.06	0.520
Grade, n (%)			0.004			
1	154 (55.8)	2 (15.4)				
2	106 (38.4)	8 (61.5)		4.13	0.81-21.07	0.088
3	16 (5.8)	3 (23.1)		10.12	1.28-81.37	0.029
MI, n (%)			0.006			
≤1/2	225 (81.5)	6 (46.2)				
>1/2	51 (18.5)	7 (53.8)		2.96	0.62-14.13	0.174
Cervical stromal invasion, n (%)			0.045			
Absent	270 (97.8)	11 (84.6)				
Present	6 (2.2)	2 (15.4)		5.38	0.67-43.50	0.114
Stage, n (%)			0.002			
IA	221 (80.1)	6 (46.2)				
IB	49 (17.8)	5 (38.5)				

Table 3. Continued

Patients, n (%)	No recurrence, (n=276) (95.5)	Recurrence, (n=13) (4.5)	Univariate	Multivariate		
			p-value	OR	95% CI	p-value
II	6 (2.2)	2 (15.4)				
Cytology			0.942			
Negative	128 (99.2)	8 (100)				
Positive	1 (0.8)	0 (0)				
Adjuvant treatment			0.015			
No	215 (77.9)	6 (46.2)				
Yes	61 (22.1)	7 (53.8)		0.77	0.15-3.98	0.756
LND			0.455			
Omitted	38 (13.8)	1 (7.7)				
Performed	238 (86.2)	12 (92.3)				

BMI: Body mass index, CA-125: Cancer antigen-125, OR: Odds ratio, CI: Confidence interval, MI: Myometrial invasion, LND: Lymph node dissection

Table 4. Cox univariate and multivariate analysis of DFS in LVSI negative early-stage endometrioid endometrial cancer patients

Covariate	Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value
Age	1.09	1.03-1.16	0.005	1.06	0.98-1.15	0.121
CA-125	1.01	0.99-1.03	0.503			
Tumor size						
≤2 cm	Ref					
>2 cm	2.53	0.68-9.40	0.167			
Tumor size, mm	1.07	1.02-1.11	0.002	1.07	1.01-1.13	0.018
Grade						
1	Ref			Ref		
2	7.12	0.89-57.07	0.065	6.19	0.75-51.16	0.091
3	38.76	3.78-397.58	0.002	12.94	1.06-157.84	0.045
Depth of MI						
≤1/2	Ref			Ref		
>1/2	6.03	1.90-19.16	0.002	2.26	0.48-10.63	0.303
Cervical stromal invasion						
No	Ref			Ref		
Yes	9.68	2.00-46.78	0.005	6.36	0.96-42.07	0.055
Stage						
IA	Ref					
IB	4.40	1.26-15.30	0.020			
II	16.45	2.98-90.71	0.001			
Adjuvant treatment						
No	Ref			Ref		
Yes	4.79	1.50-15.32	0.08	1.51	0.30-7.70	0.620
LND						
Omitted	Ref					
Performed	2.59	0.33-20.40	0.365			

DFS: Disease-free survival, LVSI: Lymphovascular space invasion, HR: Hazard ratio, CI: Confidence interval, CA-125: Cancer antigen-125, MI: Myometrial invasion, LND: Lymph node dissection

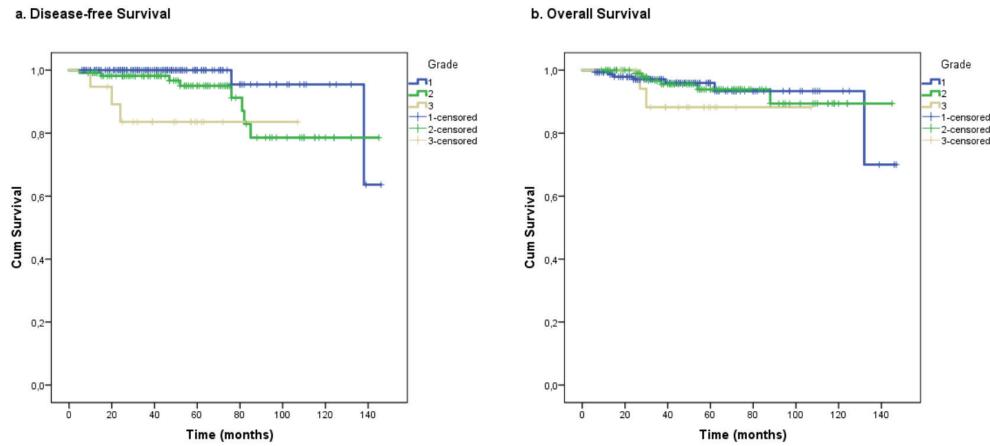


Figure 1. Kaplan-Meier estimate of disease-free survival: (a) and overall survival (b) according to grade

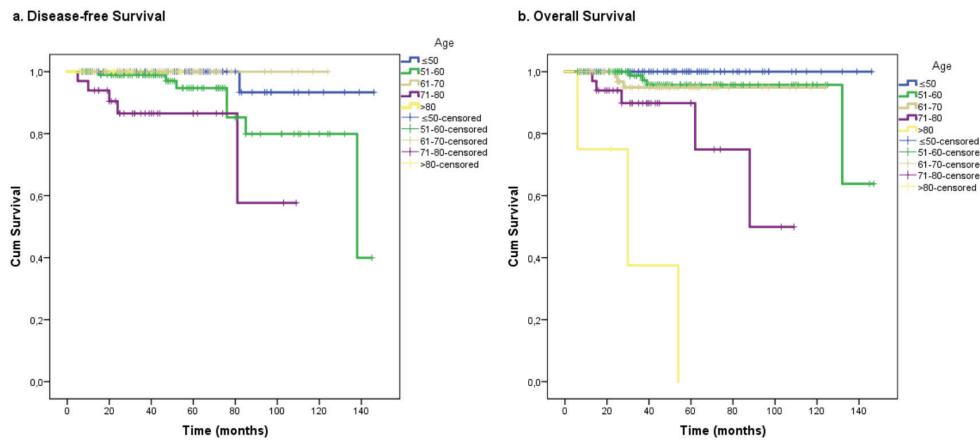


Figure 2. Kaplan-Meier estimate of disease-free survival: (a) and overall survival (b) according to age

Fifteen patients died in our study population and two of these were due to cancer recurrence. Five-year OS was 95.8%. None of the histopathological variables, nor recurrence were associated with reduced OS. Age (HR: 1.16, 95% CI: 1.09-1.22, $p < 0.001$) was found to be the only associated factor for decreased OS (Table 5) (Figure 1b, 2b).

Survival outcomes of stage I patients

Tumor size and adjuvant treatment lost their prognostic significance for recurrence after excluding stage II patients, but grade ($p=0.030$) and depth of MI ($p=0.040$) remained significant. In multivariate analysis none of the factors were independently associated with recurrence.

Five-year DFS and OS among the stage I patients were 98.2% and 96.1%, respectively. Although tumor size, grade 3 histology and depth of MI were associated with decreased DFS, none were independent factors for decreased DFS (Table 6). Only age was associated with reduced OS ($p < 0.001$).

Table 5. Cox univariate analysis of OS in LVSI negative stage I and II endometrioid endometrial cancer patients

Covariate	HR	95% CI	p-value
Age	1.16	1.09-1.22	<0.001
CA-125	1.01	0.99-1.02	0.511
Tumor size			
≤2 cm	Ref		
>2 cm	0.83	0.29-2.32	0.725
Tumor size, mm	1.01	0.97-1.05	0.737
Grade			
1	Ref		
2	0.98	0.33-2.94	0.973
3	2.23	0.46-10.89	0.322
Depth of MI			
≤1/2	Ref		
>1/2	1.40	0.44-4.47	0.572

Table 5. Continued

Covariate	HR	95% CI	p-value
Cervical stromal invasion			
No	Ref		
Yes	2.44	0.32-18.68	0.391
Stage			
IA	Ref		
IB	1.08	0.30-3.93	0.907
II	2.48	0.32-19.42	0.387
Adjuvant treatment			
No	Ref		
Yes	0.74	0.21-2.65	0.643
LND			
Omitted	Ref		
Performed	1.12	0.25-5.08	0.879
Recurrence			
No	Ref		
Yes	2.13	0.47-9.64	0.328

OS: Overall survival, LVSI: Lymphovascular space invasion, HR: Hazard ratio, CI: Confidence interval, MI: Myometrial invasion, LND: Lymph node dissection

Discussion

LVSI is established as an independent risk factor for recurrence in endometrial cancer, even in early-stages (10,16,17). To the best of our knowledge, this is the first study examining risk factors for recurrence in a cohort of LVSI negative stage I-II endometrioid endometrial cancer patients. Recurrence rate was 4.5%. Tumor size, grade, depth of MI, stage and adjuvant therapy were correlated with recurrence. However, only grade 3 disease was an independent factor associated with recurrence (OR: 10.1). Grade 3 disease, along with tumor size, was also associated with decreased DFS. Deep MI was not an independent prognostic factor for survival in LVSI negative patients in our study. In contrast, some studies found deep MI was a risk factor for distant metastasis but not for locoregional recurrence (18,19). Besides, it was found that RT improved pelvic control and DFS but not OS in stage I-II endometrial cancer patients (18,20). Thus, it may be an option to avoid adjuvant RT in early-stage low-grade LVSI negative endometrioid tumors only because of deep MI. The current NCCN Guideline indicates that BRT is preferred for stage IB grade 1-2 endometrioid tumors as adjuvant treatment, but it also states that observation can be considered when the patients are younger than 60 years and there is no LVSI (9).

Table 6. Cox univariate and multivariate analysis of DFS in LVSI negative stage I endometrioid endometrial cancer patients

Covariate	Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value
Age	1.05	0.99-1.12	0.096			
CA-125	0.99	0.96-1.04	0.904			
Tumor size						
≤2 cm	Ref					
>2 cm	1.89	0.54-6.63	0.320			
Tumor size, mm	1.05	1.00-1.09	0.043	1.03	0.98-1.08	0.216
Grade						
1	Ref			Ref		
2	4.05	0.82-19.99	0.086	3.06	0.59-15.84	0.184
3	13.13	1.72-100.37	0.013	7.62	0.91-63.74	0.061
Depth of MI						
≤1/2	Ref			Ref		
>1/2	4.19	1.21-14.51	0.024	2.11	0.54-8.28	0.284
Adjuvant treatment						
No	Ref					
Yes	3.17	0.92-10.95	0.068			
LND						
Omitted	Ref					
Performed	32.65	0.05-2043.73	0.289			

DFS: Disease-free survival, LVSI: Lymphovascular space invasion, CA-125: Cancer antigen-125, HR: Hazard ratio, CI: Confidence interval, MI: Myometrial invasion, LND: Lymph node dissection

Some authors have investigated the effect of adjuvant CT in early-stage endometrial cancer. In a current study comparing the effect of adjuvant CT versus RT in high-risk, early-stage endometrioid endometrial cancer, CT showed a trend towards lowering the distant relapse rate but the difference was not significant (21). Five-year OS and DFS rates were also similar between the groups in the same study. Similarly, in another study, it was found that adjuvant CT was associated with improved, but not significant, oncologic outcomes in stage I and II high-risk endometrioid endometrial cancer (22). Therefore, adjuvant CT appears to be an overtreatment, even for early-stage high-risk patients at given the current evidence, as it is not related with better survival rates. However, the possibility of distant metastasis along with locoregional failure should always be kept in mind for these patients.

Approximately 20% of patients with early-stage disease recur, irrespective of LVSI status (23). Although tumor size, deep MI and time from biopsy to surgery were found to be independent predictors of recurrence in stage I and II endometrial cancers, grade was the only predictor of recurrence in our study (24). We did not investigate the effect of time from biopsy to surgery, since all the patients were operated within three weeks following diagnosis.

We managed vaginal vault recurrences either by RT or surgery and intraperitoneal/distant recurrences by CT or surgery followed by CT. Complete remission after isolated vaginal recurrence is reported to be as high as 89% but distant recurrences are mostly fatal (25-27). Our results are in accordance with the literature as all patients with vaginal vault recurrences are disease free and both patients who died of disease had distant recurrences.

In our study, while 10.3% of the patients who received adjuvant treatment recurred, recurrences were seen in 2.7% of the patients who were observed. None of our patients received CT as adjuvant treatment and EBRT or BRT were applied either alone or together. Although the difference appeared significant in univariate analysis, receiving adjuvant treatment was not an independent factor for recurrence on multivariate analysis. This evidence can be explained by the fact that patients with adverse uterine factors were more likely to receive adjuvant treatment. In our study, 5 of the 13 patients with recurrence were in the low-risk group and none of these patients received adjuvant treatment. Interestingly, three of them had distant metastases (either alone or with another site) and two had intraperitoneal recurrences. All five recurrences were seen after 47 months (47-138 months) emphasizing the importance of life-time surveillance.

Since all stage II patients received adjuvant treatment, for more accurate results we performed a subgroup analysis among the stage I patients only. We found that grade and depth of MI

were both associated with recurrences. Receiving adjuvant treatment lost its prognostic significance both for recurrence and decreased DFS. With these findings, we believe that observation, rather than adjuvant RT, may be more suitable for grade 3, stage IA patients.

Although it was shown that the impact of age disappears when they are matched with younger patients with the same tumor characteristics, and prognosis of endometrial cancer is more closely associated to stage, grade, and histology rather than age, only age was found to be associated with decreased OS in our study (28,29). This finding is not surprising as our study population consisted mostly of patients with low-risk factors and recurrences were not common. Most (84%) of the relapses responded well to treatment and recurrence was not found to be an associated factor for shorter OS. There was only one recurrence in patients ≤ 50 years and none of the patients ≤ 50 years died in our study. Only two of the deaths were due to recurrences and the majority of the deaths were due to intercurrent diseases, which were mostly related to senility.

Since the recurrence rate is very low in this low-risk population, administration of adjuvant treatment is neither cost-effective nor beneficial, and also not recommended (30,31). Molecular characterization may elucidate why recurrences are seen in certain patients. Some genomic alterations, such as TP53 mutation or L1-CAM overexpression are demonstrated to be associated with greater risk of recurrence and molecular-based classification had been recently proposed in endometrial cancer (8,32,33). Therefore, by applying molecular studies, these patients may be reclassified in higher risk groups. However, future studies are needed to illuminate this issue.

Study Limitations

One of the main limitations of our study was its retrospective nature. Another limitation was the small number of events that required us to perform subgroup analysis. Also, since not all patients underwent lymphadenectomy, the small number of nodal metastases might have been missed and these patients might have been understaged. Lastly, due to the long surveillance time, adjuvant therapy indications and practices changed over time. On the other hand, the number of patients was one of the largest that had been reported with long follow-up time. All patients were operated by the same gynecologic oncologists and specimens were reviewed by gynecologic pathologists.

Conclusion

Recurrence rate was low among women with LVSI negative, early-stage endometrioid endometrial cancer and age was the only prognostic factor for shorter OS. In contrast, grade 3 histology and tumor size were independent factors associated

with decreased DFS. Although distant metastases were more common in this group of patients and may be fatal, most of the recurrences were cured. Therefore, even in the presence of risk factors, observation without adjuvant treatment may be the optimal management.

Ethics Committee Approval: *The study protocol was reviewed and approved by Ankara University Faculty of Medicine Clinical Research Ethics Committee (approval number: 10-420-14, date: 09.06.2014).*

Informed Consent: *A written informed consent was obtained from all the patients in order to use their medical data for scientific purposes.*

Peer-review: *Externally peer-reviewed.*

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Comparison of transumbilical and periumbilical median incisions in ovarian cancer surgery

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Abstract

Objective: The umbilicus is traditionally circumvented while performing a vertical midline abdominal incision. There is a gap in knowledge pertaining to avoiding the umbilicus. Our aim was to investigate whether a transumbilical (TU) or periumbilical (PU) midline incision conferred any advantage to the patient.

Material and Methods: This was a retrospective cohort study of patients undergoing ovarian cancer surgery with a midline incision, from the pubic tubercle to the xiphoid. All surgery was performed by the same team of gynecological oncologists. Patients were classified into two groups according to the midline incision used, TU or PU. The primary endpoint was the incision wound complication rate.

Results: TU and PU midline incisions were performed in 54 and 68 patients, respectively. There were no differences between the two groups in terms of patient characteristics and operative details. The two groups had comparable rates of complications, including wound infection (7.4% vs. 10.3%, $p=0.75$), deep surgical site infection (11.1% vs. 4.4%, $p=0.18$), evisceration (3.7% vs. 4.4%, $p=0.99$) and incisional hernia (33.3% vs. 33.8%, $p=0.99$).

Conclusion: Our findings suggest that circumventing the umbilicus during laparotomy did not have any advantage. Future prospective randomized trials are warranted to validate this finding. (J Turk Ger Gynecol Assoc 2023; 24: 271-6)

Keywords: Gynecologic oncology, incisional hernia, infection, ovarian cancer

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Introduction

The most important consideration when choosing the type of incision for surgery is to provide adequate exposure. Postoperative wound healing, pain, cosmetic concerns and complications, such as hernia risk, should also be considered. A properly placed incision of sufficient length will facilitate minimal tissue trauma, complete haemostasis, proficient use of retractors, and efficient visualization (1). Ovarian cancer surgery, whether primary or recurrent, is one of the most comprehensive operations due to the tumor spread pattern. It requires a wide incision for exploration, staging and debulking of both upper and lower abdomen implants. The vertical midline incision provides access to the abdominal viscera, liver, spleen, inferior vena cava, aorta, kidneys, pelvic organs

and related lymphatics that may be sites of ovarian cancer metastasis (2).

The umbilicus is traditionally circumvented when conducting a midline laparotomy, although the reason for this is unclear, possibly to reduce the risk of wound infection and incisional hernia. To the best of our knowledge, only one study on this subject has been published and, according to this report, the method of avoiding the umbilicus in midline laparotomy served no useful purpose (3). However, it was reported that when circumventing the umbilicus it was difficult to perform a symmetrical curve around the umbilicus.

Thus, there is insufficient published evidence to understand if the periumbilical (PU) midline incision is beneficial or not. The present study was conducted to determine whether outcomes after the use of the transumbilical (TU) incision differed from



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the PU incision, in terms of surgical site infection, incidence of incisional hernia and cosmetic appearance.

Material and Methods

Trial design

Approval for the study was obtained from the İstanbul University, İstanbul Faculty of Medicine Clinical Research Ethics Committee (approval number: 08, date: 02.04.2021). Between January 2016 and December 2019, patients who underwent a laparotomy for ovarian cancer surgery with a vertical midline incision, from the pubic tubercle to the xiphoid, were reviewed retrospectively. Patients who met the criteria were classified into two groups according to the type of midline incision, TU or PU (Figure 1). Figure 2 depicts the flow diagram and architecture of the retrospective cohort study.

Participants

Participants aged between 18 and 80 years were included. Patients who had a prior history of incisional or umbilical hernia before the index surgery and patients who were lost during the follow-up within 12 months of the operation, were not included. Patients who had a relaparotomy due to complications, such as anastomotic leak and whose fascia was not closed, were also excluded.

Surgical technique

Preoperative mechanical bowel preparation was used in all patients. Antibiotic prophylaxis was given, and povidone-iodine was used for antiseptis of the skin. The same team of gynaecologic oncologic surgeons performed all of the operations through a midline laparotomy. The team consisted

of eight surgeons in total. Each surgery was performed by a senior consultant and a fellow, drawn from this pool of surgical staff. Laparotomy was performed with a scalpel for skin incision through the middle of the umbilicus (group TU) or from the left side of the umbilicus (group PU), extending from the pubic tubercle to the xiphoid; followed by diathermy in cut mode for the subcutaneous tissue. For patients who previously had surgery at the planned incision site, the incision was made through the previous scar. A limited amount of fascia was opened by a scalpel. The preperitoneal fat was bluntly dissected from the peritoneum by sweeping the index finger. Once it was marked, the peritoneum was raised with forceps and opened longitudinally with scissors. After the peritoneal cavity had been entered, the fascial incision was completed



Figure 1. Transumbilical and periumbilical midline incisions

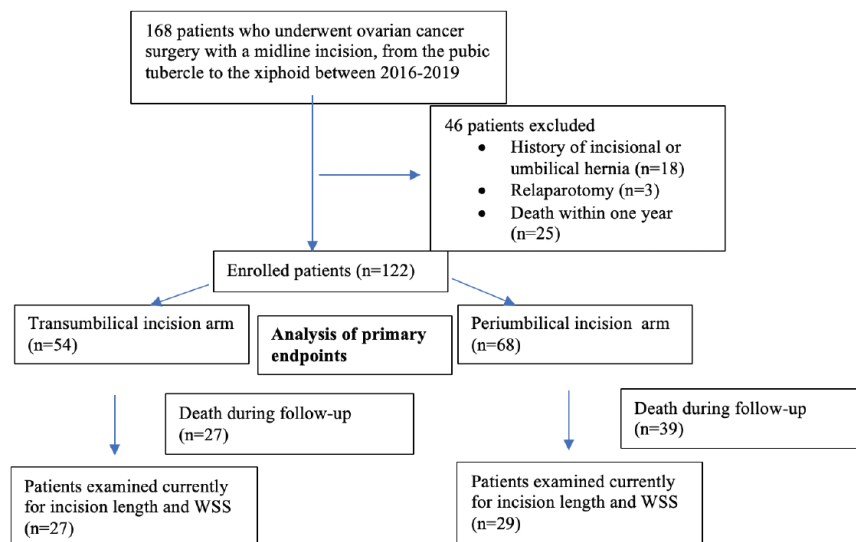


Figure 2. Flow diagram
 WSS: Wound satisfaction score

by diathermy in cut mode. When extending superiorly, the ligamentum teres was encountered and taken between clamps, divided, and ligated to expose the liver. Bleeding points were controlled by coagulation diathermy. For exploration, a Thompson retractor was used. After the operation for ovarian cancer, whether primary or recurrent, we used a continuous-suture technique for closing the fascia in one layer with slowly absorbable monofilament suture, polydioxanone (PDS) no 1. Subcutaneous tissue was closed with absorbable multifilament polyglactin no. 2-0 and skin was closed with metal staples. A drain was put in a Douglas pouch. Subcutaneous drains were not used.

Until the patients were discharged, all wounds were examined daily. Patients were asked to use an abdominal corset for six weeks postoperatively. The metal staples were removed between the fourteenth and twenty-first postoperative days. Patients were followed up every three months according to our ovarian cancer follow-up protocol, and magnetic resonance imaging (MRI) and/or computed tomography (CT) scan was performed in the first year after the surgery.

Data collection

Demographic characteristics, serum albumin levels, the American Society of Anesthesiology score of patients, type of surgery, intraoperative details, the duration of hospital stay and early (within 30 days) postoperative complications, including infection or evisceration were noted. While grouping the operation type, primary surgery was considered together with whether neoadjuvant chemotherapy was administered or not. Those who received preoperative chemotherapy, regardless of primary or recurrent surgery, were considered to have had neoadjuvant chemotherapy. A wound infection was described as pus discharge. The presence of wound dehiscence without evisceration was also considered a sign of wound infection. During the 12-month follow-up, the presence of incisional hernia was evaluated. If a fascial defect (along the incision) was detected by imaging (CT or MRI) in the first year, it was noted as an incisional hernia.

Patients still alive were called for examination and informed consent was obtained. Incision length was measured and they were asked to score the appearance of the scar on a scale from 1 to 10 using a wound satisfaction score [(WSS); higher scores represent greater satisfaction].

Primary endpoints

The primary objective was to compare the two types of incisions in terms of wound infection and incisional hernia. The secondary endpoint was patient satisfaction regarding their scars.

Statistical analysis

The SPSS, version 21.0 was used for all statistical analyses (IBM Inc., Armonk, NY, USA). Data are expressed as mean \pm standard deviation or median and range for continuous variables, as appropriate, and categorical values are expressed as absolute numbers and percentages. Comparison of categorical variables was performed using Fisher's exact test and Yates continuity correction. Comparison of continuous variables first required the evaluation of data normality. Normally distributed data was compared using an Independent-samples t-test while abnormally distributed data was compared using the Mann-Whitney U test. A $p < 0.05$ was considered statistically significant.

Results

Patients' characteristics

The medical records of 168 patients were analysed and 46 patients were eventually excluded, leaving a study cohort of 122 patients. TU and PU midline incisions were performed on 54 (44.3%) and 68 (55.7%) patients, respectively (Figure 2). There were no significant differences between the two groups in terms of patient characteristics and operative data, as shown in Table 1, 2.

Overall, 4% (5/122) of the patients had chronic pulmonary disease, 26% (32/122) had hypertension and 12% (15/122) had diabetes mellitus. There were no significant differences in procedures and neoadjuvant treatments between the two groups. Hyperthermic intraperitoneal chemotherapy was administered to a total of eight patients. All patients received chemotherapy (platinum-based regimen) postoperatively, three refused to complete treatment and four interrupted because of toxicity. A total of 36 (29.5%) patients had a history of midline incision, 27 of which were due to previous ovarian cancer surgery. More patients in the PU group had a history of midline incision than in the TU group (36.8% vs. 20.4%) but this did not reach significance ($p = 0.08$).

Primary outcome

The two groups had comparable rates of early wound complications, including wound infection (7.4% vs. 10.3%, $p = 0.75$), deep surgical site infection (11.1% vs. 4.4%, $p = 0.18$) and evisceration (3.7% vs. 4.4%, $p = 0.99$). Incisional hernia occurred in 33.6% (41/122) with no significant difference between the two groups (33.3% vs. 33.8%, $p = 0.99$).

Secondary outcome

Sixty-six patients had died of cancer by the time the study was scheduled. The surviving patients (45.9%) reported no disparity in WSS between the two groups (5 vs. 5, $p = 0.15$).

Table 1. Characteristics of patients

	Transumbilical, (n=54)	Periumbilical, (n=68)	p
Age, years	51.7±13.9	54.2±11.2	0.29
Parity	2 (0-12)	2 (0-10)	0.58
BMI, kg/m ²	28.6±6.0	26.9±5.7	0.30
Smoking, n (%)	8 (14.8)	5 (7.4)	0.30
Neoadjuvant chemotherapy, n (%)	13 (24.1)	16 (23.5)	0.99
Menopause status, n (%)			
Premenopausal	24 (44.4)	20 (29.4)	0.13
Postmenopausal	30 (55.6)	48 (70.6)	
Preoperative serum albumin level, mg/dL	3.68±0.79	3.90±0.52	0.92
ASA score (3-4), n (%)	10 (18.5)	14 (20.6)	0.96
Diabetes mellitus, n (%)	4 (7.4)	11 (16.2)	0.17
Hypertension, n (%)	16 (29.6)	16 (23.5)	0.58
Ascites, n (%)	50 (92.6)	67 (98.5)	0.17
History of midline incision, n (%)	11 (20.4)	25 (36.8)	0.08
BMI: Body mass index, ASA: American Society of Anesthesiologists			

Table 2. Operative data of patients

	Transumbilical, (n=54)	Periumbilical, (n=68)	p
Type of operation, n (%)			
Primary	46 (85.2)	49 (72.1)	0.13
Recurrence	8 (14.8)	19 (27.9)	
HIPEC, n (%)	2 (3.7)	6 (8.8)	0.30
Duration of surgery, minutes	240 (30-720)	233 (60-600)	0.48
Bowel resection, n (%)	18 (33.3)	18 (26.5)	0.53
Stoma, n (%)	11 (20.4)	11 (16.2)	0.72
Hospitalization period, day	8 (2-26)	6 (2-21)	0.71
Wound infection, n (%)	4 (7.4)	7 (10.3)	0.75
Surgical site infection (except the wound), n (%)	6 (11.1)	3 (4.4)	0.18
Evisceration, n (%)	2 (3.7)	3 (4.4)	0.99
Incisional hernia, n (%)	18 (33.3)	23 (33.8)	0.99
Incision length, cm	30 (23-33), (n=27)	30.5 (24-35), (n=29)	0.16
Wound satisfaction score	5 (1-7), (n=27)	5 (3-10), (n=29)	0.15
HIPEC: Hyperthermic intraperitoneal chemotherapy			

Discussion

The origin of the widely-held notion that circumventing the umbilicus is beneficial during a midline abdominal incision is unclear. There is a belief that TU incisions have the potential to increase the rate of surgical site infection, since the umbilical dimple causes moisture to collect and stagnate, allowing bacteria to colonize (4). In the present study, the TU midline incision was found to be as safe as the PU incision. To date, only one study focusing on laparotomy and comparing circumbilical and TU incisions has been performed (3). In that prospective randomized study, 109 patients from the general surgery

department were enrolled and were randomly allocated to the TU abdominal incision group or the circumumbilical abdominal incision group. Wound infections occurred in 9 of 58 (15.5%) patients who had TU incisions and 8 of 51 (15.7%) patients who had circumumbilical incisions. These authors reported that avoiding the umbilicus during the incision had no impact on the risk of infection. Later, as laparoscopy became more common, studies on TU and PU incisions for laparoscopic access were conducted. The initial peritoneal access is a crucial aspect of laparoscopic surgery. Five randomized controlled trials, involving 783 patients, were examined in a meta-analysis to investigate whether the initial umbilical trocar was better

through a TU or PU (infra or supraumbilical) incision. There were no major differences in the rates of complications, including surgical site infection or umbilical hernia, between both groups (5). In our series, the overall surgical site infection rate, including deep and superficial infections, was 14.7% (10/68) in the TU group vs. 18.5% (10/54) in the PU group PU which was not significantly different.

Hamzaoglu et al. (6) identified the umbilical flora and microorganisms that caused trocar site infection. Prior to laparoscopic surgery, these authors took swabs from the umbilical dimple before and after antiseptics of the skin with povidone-iodine, and from the infection site if infection was present. Povidone-iodine was found to be effective in removing microorganisms from the umbilical dimple in 89 of 100 patients. Despite being isolated after antiseptics, bacteria isolated before and after antiseptics did not cause wound infection. They concluded that povidone-iodine is an effective antiseptic and that pathogens acquired in hospitals cause trocar site infection, rather than the umbilical flora.

Incisional hernia of the umbilicus is also a cause for concern. In the study of Paes et al. (3), comparing TU and circumumbilical abdominal incisions, surviving patients were followed for at least one year, and three of the 109 patients had incisional hernias with no difference between the two groups. In the present study, incisional hernia was encountered in 33.6% of all patients. Personal and technical risk factors for fascial disruption including age, ascites, major surgery, malignancy, type and length of incision (7), presumably contributing to the high incidence of hernia in our patients. These risk factors were all similar between both groups of patients and there was no difference in hernia rates between the PU and TU groups. The transit pass through the umbilicus was supposed to shorten the incision. The length of incisions of the surviving patients were measured, and again there was no difference between the groups.

In our series, no surgeon had any difficulty accessing the abdomen through a TU incision, as had been previously reported by Paes et al. (3). Since it was cancer surgery, the operation times were long (mean time 4 hours) in the present study, which did not make the rapidity of access achievable with the TU incision type very noticeable, but it may lead to faster access to the abdomen in emergency operations. Sutures were inserted and removed with difficulty inside the umbilicus, but Paes et al. (3) reported that the wounds healed without the need for skin sutures at the base of the umbilicus.

Vertical midline incision *per se* was associated with poor cosmetic results (8). The satisfaction with the appearance of the wound was rated to be similar by both groups of patients. No patient was asked whether the TU or PU incision was better,

and the complaints were due to the length of the incision scar rather than the appearance of the umbilicus.

Study Limitations

There were strengths and weaknesses of our study. Our research had the advantage of filling a gap in the literature regarding the effects of a TU midline incision and these results may lead to a change in practice. The major limitation of our study was its retrospective design. Due to the complexity of our patients' conditions, there might be a bias in the assessment of outcomes, and it may be more appropriate to evaluate the outcomes of TU incision in less complex surgery.

Conclusion

To summarize, both the present study and an earlier similar study found that passing through the umbilicus had no negative consequences. Furthermore, studies based on laparoscopy have shown that the umbilical incision was a relatively risk-free procedure. Avoiding the umbilicus during laparotomy provided no benefit. Passing through the umbilicus is a safe and feasible method. It may be simpler and faster to perform a TU abdominal incision. However, to validate these findings and provide evidence for a wider change in surgical practice, randomized prospective trials are required.

Ethics Committee Approval: *The study protocol was reviewed and approved by İstanbul University, İstanbul Faculty of Medicine Clinical Research Ethics Committee (approval number: 08, date: 02.04.2021).*

Informed Consent: *Patients still alive were called for examination and informed consent was obtained.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Surgical and Medical Practices: H.Y.Ç., H.S., E.Ç., Y.S., S.T.; Concept: H.Y.Ç., H.S.; Design: H.Y.Ç., H.S.; Data Collection or Processing: M.M.C.; Analysis or Interpretation: H.Y.Ç., Y.S., S.T.; Literature Search: H.Y.Ç., H.M.B.; Writing: H.Y.Ç.*

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Comparison of the effect of dietary and herbal supplements on anthropometric, metabolic and androgenic profiles of women with polycystic ovary syndrome: a systematic review and network meta-analysis protocol

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Abstract

Polycystic ovarian syndrome (PCOS) is characterized by obesity, glucose intolerance, dyslipidemia, and hyperandrogenemia. Although several, placebo-controlled 2x2 factorial design, randomized controlled trials have tested the efficacy of dietary and herbal supplements in controlling these parameters in PCOS patients, these studies are not suitable for a comparative efficacy assessment across these supplements. Herein, a protocol for systematic review and network meta-analysis (NMA) is presented to make such a comparison. PubMed, Embase, and Scopus, were interrogated to identify relevant trials, published in English, factors to be investigated will include dietary factors, micronutrients, choline, essential fatty acids, and herbal extracts. Other factors to be considered include trial design, population characteristics, interventions compared, and outcomes of interest. The revised Cochrane tool was used for the appraisal of eligible trials. NMA (frequentist method) will be used for respective outcomes to compare effect sizes (weighted or standardized mean difference) among the interventions. Both logical and statistical (inconsistency assessment) approaches will be used to minimize intransitivity risk. The surface under the cumulative ranking curve values will be used to gauge the best intervention for outcomes with a statistically significant effect size suggesting a favorable outcome. Additionally, the exploration of interrelation among interventions and the small study effect in respective NMA models will be investigated using network maps and comparison-adjusted funnel plots, respectively. Statistical significance is assumed at $p < 0.05$ with 95% confidence interval. Stata statistical software (v16) was used for analysis. The study was registered with PROSPERO, registration number: CRD42022301530. (J Turk Ger Gynecol Assoc 2023; 24: 277-83)

Keywords: Polycystic ovary syndrome, dietary supplements, herbal medicine, glucose metabolism disorders, lipid metabolism disorders, body weights and measures, hyperandrogenism

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Introduction

Polycystic ovarian syndrome (PCOS) is the most common endocrinological disorder of reproductive-age females. Depending on the diagnostic criteria used, its prevalence ranges between 5-15% (1). PCOS is a constellation of diverse clinical features, among which obesity, metabolic abnormalities, and hyperandrogenism are central (1). Pathophysiologically, these

features are interconnected, and one can aggravate the other. Epidemiological and genetic studies suggest an intricate association between PCOS and obesity, which is not fully understood (2). Obesity in women with PCOS increases the risk of hyperandrogenemia, via insulin resistance (IR) (1), infertility (particularly with abdominal obesity) (3), and preterm births (4). In terms of metabolic abnormalities, IR is a major metabolic complication in patients with PCOS. Nearly



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two-thirds of PCOS patients have abnormal IR (1). IR-led hyperinsulinemia increases the risk of type 2 diabetes mellitus (T2DM) and impaired glucose tolerance in women with PCOS (1,5,6). Dyslipidemia is another key metabolic derangement in PCOS and can present with low levels of high-density lipoprotein (HDL) and high levels of triglyceride and low-density lipoprotein (LDL) (7-9). Hyperandrogenism in patients with PCOS is also associated with IR. IR-led hyperinsulinemia decreases sex hormone-binding globulin (SHBG) levels, which in turn increases the peripheral availability of free androgen and its consequent peripheral action (7). Hyperandrogenism can present clinically with hirsutism, acne, virilization, infertility, and alopecia (10). The biochemical presentation of hyperandrogenism includes elevated levels of testosterone, high free androgen index [(FAI) defined as the testosterone to SHBG ratio], and increased adrenal androgens, such as dehydroepiandrosterone sulfate (DHEAS) (10).

Contemporary treatments and their limitations

Presently, there is no cure for PCOS, and the treatment is symptom-directed (7). For weight loss and IR, the treatment choices include life style modification, bariatric surgery, weight loss-inducing drugs, and insulin-sensitizing drugs. Hormonal contraceptives are used for androgen-related symptoms. However, these PCOS managements are not supported by rigorous evidence and are often expert consensus-based and may not be suitable for all patients with PCOS. Although the consensus favors hypocaloric diet consumption for weight loss in PCOS patients, evidence remains unclear if any particular dietary formulation benefits weight loss or metabolic changes (7,11,12). Moreover, nearly 95% of PCOS patients undergoing weight loss experience relapse (7). A 2019 Cochrane review of randomized controlled trials (RCTs) reported a modest dip in body weight and body mass index (BMI) with lifestyle interventions (13). However, the reviewers categorized the evidence as low quality due to the high or unclear risk of bias (RoB) in the reviewed trials (13).

While it is believed that the benefits of exercise in PCOS patients are the same as in women with T2DM, there is no robust evidence in PCOS (7). Moreover, exercise is not an option for PCOS patients with locomotor disabilities. Despite the growing popularity of bariatric surgery for weight loss, it is presently of limited use for overweight and obese women with BMI ≥ 40 kg/m² (14), and many cannot afford it, if not available in national health programmes (15). In terms of weight loss-inducing drugs, there are inadequate efficacy data and safety concerns with certain drugs, such as Sibutramine and Rimonabant, which are not endorsed in the USA (7,16,17).

Among the insulin-sensitizing drugs, metformin is the only insulin-sensitizing drug recommended in PCOS, in patients not suffering from T2DM (18). Although metformin helps with weight loss, reducing IR, and mildly improving androgen-related symptoms (1), its role in diabetes prevention in patients with PCOS is not well-established due to the shortage of adequately powered studies of long duration (7).

While oral contraceptive pills are used for controlling androgenic effects, these are not ideal in women with PCOS who are planning to conceive or those with a history of smoking, obesity, hypertension, or clotting disorders (7).

The purpose of this study

Given these limitations of contemporary PCOS management, research for novel alternative or adjunct therapies are essential. Several RCTs have investigated the role of various dietary supplements and herbal extracts on the anthropometric, metabolic, and androgenic markers in PCOS. For instance, trials in PCOS patients testing the role of chromium (19), cinnamon (20), *Salvia officinalis* extract (21), and flaxseed (22) supplementation improved certain glycemic and lipid parameters, such as insulin levels and LDL concentrations, respectively. The trials supplementing cinnamon (20) and flaxseed (22) in PCOS found no significant decrease in testosterone levels, but quercetin (23) supplementation was reported to decrease testosterone levels. However, the comparative efficacy of these supplements remains unclear, due to the 2x2 placebo-controlled factorial design of such trials. An across-supplement comparison would allow healthcare professionals to choose the optimal supplement or supplement mix for controlling clinical and biochemical parameters of interest in PCOS patients and deliver more patient-specific care.

Therefore, this systematic review and network meta-analysis (NMA) protocol was performed and the results are presented here to juxtapose the efficacy of various dietary supplements and herbal extracts in controlling body weight, BMI, waist circumference, markers of blood glucose and lipid metabolism and androgenic markers. A complete list of interventions and outcomes of interest are listed below. The protocol for this proposed systematic review is presented below.

Methods

The protocol adheres to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) (2015) guidelines (Supplement 1) (24). This protocol was registered with PROSPERO (registration no: CRD42022301530) (25).

Eligibility criteria**Inclusion criteria**

a. Trial population: Women of any age with PCOS. The diagnosis of PCOS will get accepted as per the trialists.

b. Trial design: Irrespective of treatment duration and the number of intervention arms, parallel-arm RCTs were eligible for inclusion.

c. Intervention arm: Women in the treatment arm/s should have been receiving at least one of the following oral interventions;

1. Dietary factors: L-carnitine, coenzyme Q10, lipoic acid, probiotics, synbiotics, and phytochemicals will be included. The following phytochemicals will be considered-chlorophyll and chlorophyllin, carotenoids, curcumin, garlic, indole-3-carbinol isothiocyanates, fiber (such as psyllium or included with prebiotics), phytosterols, flavonoids (e.g. quercetin), soy isoflavones, lignans, resveratrol.
2. Micronutrients to be considered include: water- and fat-soluble vitamins and minerals such as calcium, copper, selenium, chromium, iron, magnesium, manganese, molybdenum, phosphorus, iodine, potassium and zinc.
3. Choline.
4. Essential fatty acids (e.g. omega-3 fatty acids).
5. Herbal extracts (e.g. thylakoid).

The dosage and regimen of these interventions, as stated by the trialists, will be accepted. Trial participants receiving a combination of these supplements will also qualify.

d. Comparator arm: The control arm must receive standard PCOS care (with or without placebo).

e. Outcomes:

1. Glycemic markers: fasting plasma glucose, homeostasis model assessment of IR, insulin, glycated hemoglobin, and quantitative insulin sensitivity check index.
2. Lipid markers: HDL, LDL, and very LDL, triglyceride, and total cholesterol.
3. Anthropometric indices: weight, BMI, and waist circumference.
4. Sex hormones: DHEAS, follicle-stimulating hormone, luteinizing hormone, testosterone, SHBG and FAI.

The above list of interventions and outcomes of interest cannot be exhaustive because trialists continue testing newer supplements and biochemical markers. Therefore, this list was prepared based on prior knowledge and scrutiny of relevant contemporary trials (accessible utilizing the pilot search strategy depicted below). Preparation of the outcomes list was based on clinical relevance in PCOS. However, given the large number of interventions and outcomes that may be tested in different future clinical trials, we will include additional relevant interventions and outcomes that emerge during the study selection stage of the review.

Exclusion criteria

- a. Trials in pregnant or lactating females.
- b. Trials in women with endocrinopathies mimicking PCOS (e.g., Cushing's syndrome, androgen-producing tumors, non-classic adrenal hyperplasia, and pharmacologically induced androgen excess).

Information sources and search strategy

We will search for eligible trials published in the English language in the PubMed, Scopus, and Embase databases since the conception of these databases, irrespective of the publication date and geographic origin of the study. A draft search string for searching the PubMed database is as follows: ("polycystic ovary*" [Title/Abstract] OR "PCOS" [Title/Abstract] OR "stein leventhal" [Title/Abstract] OR "stein leventhal" [Title/Abstract] OR "Sclerocystic Ovarian" [Title/Abstract] OR "Ovarian Degeneration" [Title/Abstract] OR "Sclerocystic Ovaries" [Title/Abstract]) AND (controlledclinicaltrial[Filter]). This search string was considered appropriate (26) as it retrieved five, pre-identified eligible citations (Supplement 2) (19-23). Using identical search strings, the other databases will also be interrogated. Supplementary searches will take place in the bibliography of the articles included in the review.

After uploading the retrieved citations into Rayyan, a systematic reviewing software, duplicate citations will be excluded, and then, the remaining articles' titles and abstracts will be skimmed for eligibility (27). A full-text reading will occur for articles that may be included or those deemed unlikely to be included. A list of excluded articles will be kept, following the full-text reading and the list will include reasons for exclusion.

Data abstraction

The following data items will be abstracted, primarily in a data abstraction form (weblink):

1. The following study details will be collected for each trial: first author's last name, date of publication, country of conduct, single or multicentered, trial identification details, ethics information, participant consent, and funding sources.
2. Characteristics of the study population to be collected will include: The number of PCOS patients in each intervention arm and their ages, the diagnostic criteria used to diagnose PCOS, BMI of participants in respective intervention arms, and the PCOS treatment participants were receiving in addition to the interventions being tested.
3. The intervention tested in the respective treatment arms of the reviewed trials will be noted, along with dosage, frequency of administration, and duration of intake.
4. In the data abstraction form (weblink), outcomes of interest for which the trialists reported outcome data will be recorded. In a separate form, analytic data gathering will happen from respective trial arms (Supplement 3).

Risk of bias in individual studies

The RoB assessment will be performed for respective studies using the Revised Cochrane RoB 2 tool for randomized trials (28). Signaling questions assessing the following domains will be answered to determine their bias: the method of randomization, interventions aimed to be studied, unavailable outcome data, measurements of the outcome data, and reported results. The review authors will assess the appropriateness of the electronic algorithm-generated bias for each of the domains and modify it if they feel necessary. An overall assessment will be performed for each study, based on the judgment made for respective domains (described elsewhere) (28).

Three or more authors will perform the review. They will carry out study selection, data abstraction, and the RoB assessment individually, and subsequently collate their findings. All conflicts in an opinion between review authors will be resolved by discourse and a third-party opinion will be sought if the latter doesn't achieve consensus.

Network meta-analysis

Using the endpoint average and their standard deviations (SD), we will conduct NMA (frequentist methods) to compare treatment effects across the interventions. The NMA models will source data from trial arms that have tested a combination of supplements in these combined forms so that these interventions can be contrasted with other mono- or co-supplemented forms. For instance, vitamin D sole administration and vitamin D-calcium simultaneous administration forms will be included in the NMA models in these respective forms and not as a unique vitamin D supplementation group.

Outcome selection criteria for network meta-analysis

An outcome will be considered eligible for NMA when it meets the criteria listed below (26,29,30):

1. Low heterogeneity: Outcomes for which a pairwise meta-analysis (PMA)-based comparison between intervention recipients and non-recipients suggest low heterogeneity risk will be incorporated in the NMA models. Heterogeneity detection and quantification will be made using Chi² statistics (statistically significant at p<0.1) (31) and I² values (of which 25, 50, and 75% are interpreted as low, moderate, and high heterogeneity, respectively) (32).

This statistical inconsistency evaluation will occur if these PMA models include a minimum of 20 studies or an average study population size of ≥80 (for adequately powered (80%) analysis) (33). The meta-analysis model choice, fixed-effect versus random-effect (DerSimonian and Laird), will depend on the methodological diversity among the trials included in

the review, and an appraisal of this will include consideration of features such as baseline demographic characteristics, treatment duration, the design and setting of the clinical trials, and PCOS-diagnostic criteria.

We will combine the endpoint means and their SDs across intervention arms of trials testing the effect of dietary supplements in >1 intervention arm using equations (31) 1 and 2-

$$\text{Mean} = \frac{(n_1m_1+n_2m_2)}{n_1+n_2} \quad (1)$$

$$\text{SD} = \sqrt{\left(\frac{n_1-1}{n_1+n_2}\right)sd_1^2 + \left(\frac{n_2-1}{n_1+n_2}\right)sd_2^2 + \left(\frac{n_1n_2}{n_1+n_2}\right)(m_1^2 + m_2^2 - 2m_1m_2)/((n_1 + n_2) - 1)} \quad (2)$$

where,

n1, n2: sample sizes of hypothetical sample sizes of treatment arm 1 and treatment arm 2, respectively,

m1, m2: average value of treatment arm 1 and treatment arm 2, respectively,

sd1, sd2: SD of m¹ and m², respectively.

2. A connected network must be formed for each outcome.
3. The heterogeneity's degree of freedom should allow a consistency model fitting (random effect).
4. The degree of freedom of the inconsistency should allow for an inconsistency model fitting.

We will perform a random-effect NMA to allow for heterogeneity as it is not possible to guarantee that the trials randomized by intervention will be exclusively identical in trial characteristics (e.g., study population characteristics or trial design) (34).

Transitivity and consistency

To ensure the validity of indirect comparisons (transitivity) when including several RCTs in an NMA model, we will check if the studies are identical in all aspects except the compared interventions (35-38).

To decrease intransitivity risk, the eligibility criteria of the proposed study are framed in such a manner that the trials are primarily different in the tested interventions only (38,39). For instance, as the bioavailability of the supplements and their consequent effect on the outcomes may vary with various routes of administration, trials using it in patients with PCOS and given orally will only get integrated in the proposed review. Similarly, trials in conditions mimicking PCOS will also not be selected.

The statistical transitivity assessment will include local and overall inconsistency evaluation (40). Network inconsistency resulting from transitivity assumption violation will be assessed using local and global inconsistency evaluations. The local node-splitting method will test inconsistency among respective intervention pairs (40). We will accept a network consistency assumption when both the local and overall inconsistency evaluations are suggestive of no inconsistency.

Network map

Using network maps, a visual assessment of the interventions compared in the NMA models will be undertaken. In each NMA model, the nodes will depict the interventions compared, and its width will increase as more trial participants receive it. The number of participants contributing to the formation of respective nodes of the network maps will be presented in tables. The node-connecting lines in the network map will depict the trials comparing two interventions (represented by nodes), which thickens as more trials compare these. If the network maps are too complex to interpret, due to excessive crisscrossing, we will attempt to decrease the intricacy by repeated swapping of treatment pairs (41).

Effect size

For PMA and NMA, the effect size estimation will be performed using weighted or standardized mean differences based on similarities or dissimilarities in reporting units across the trials, respectively (42).

A statistically significant effect size will determine the relative superiority among the compared interventions. A negative effect size will be considered favorable for an outcome in which a reduction in values is the anticipated outcome (e.g., fasting plasma glucose) and *vice versa*.

Obtaining SD in special circumstances

We will use formulas 3 or 4 to calculate SD from standard error or 95% CI, respectively (31).

$$SD = SE \times \sqrt{n} \text{-----} (3)$$

$$SD = \sqrt{n} \times \frac{(\text{upper limit} - \text{lower limit})}{3.92} \text{-----} (4)$$

where *n* and SE are the sample size and standard error; 3.92 (2x1.96) SE was used for 95% confidence interval (CI); 3.29 and 5.15 can be used instead of 3.92, if reporting occurs at 90 or 99% CI, respectively (31). The CI values of 3.92, 3.29, or 5.15 will be substituted by slightly larger value derived from the specific t distribution when the respective treatment arms are made up of small sample sizes (*n*<60) (31).

League tables and ranking probabilities

In league tables, the effect sizes derived from the NMA of respective outcomes will be presented, with diagonal cells of these tables representing the interventions contained in the NMA models.

Our assessment of the best intervention will include the usage of the surface under the cumulative ranking curve values, which can range between 0-100%, with higher values representing superior interventions (43). This will be performed

for outcomes with statistically significant effect sizes, as suggested by the league tables.

RoB across studies

As all trials included in the proposed review will compromise of a comparator arm receiving standard PCOS care with or without a placebo, the small study effect will be judged using comparison-adjusted funnel plots (44,45). Plots with asymmetry will suggest deviation in effect sizes among studies with large and small sample sizes (45).

Sensitivity analysis

The following sensitivity analysis will occur to ensure the robustness of the primary NMA:

1. If an NMA model included trials with a high RoB component, the repeat NMA will not incorporate these trials. It will help distinguish the latter’s effect on the main NMA findings.
2. The NMA about androgenic markers will be iterated after eliminating trials conducted on menopausal women, as hyperandrogenism tends to resolve in PCOS patients nearing their menopause (46). Women ≥45 years will be considered in the menopausal age groups unless clarified in the trial (47).
3. As the method of diagnosis of PCOS remains unclear in pre-pubertal and peri-pubertal girls (5,7), preliminary analyses will be repeated following the exclusion of trials in women aged ≤19 years (as peri-puberty is up to adolescence, i.e., age 19 (48,49).
4. To evaluate if short duration trials (≤12 weeks) have affected the NMA findings, the NMA will be reiterated, eliminating any short duration trials.

Additional analysis

NMA will be performed for respective outcomes using data from trials with overweight and obese participants only, to disentangle the effects of dietary and herbal supplements in this patient population.

Risk of bias across studies

We will use comparison-adjusted funnel plots to assess publication bias. This assessment will be feasible as trials included in this review will have a common comparator arm receiving a placebo and/or standard care (50). Plots depicting asymmetry would indicate a variation between small and large RCTs (44,45).

Analytic tools

We will conduct the pairwise and NMA in the Stata statistical software version 16.0 (StataCorp, College Station, Texas, USA) using the meta and network packages, respectively, and determine the statistical significance of the effect sizes at a p-value of <0.05 and 95% CI.

Conclusion

Reporting of the review

The PRISMA statement for NMA will be followed for reporting of the completed review (51).

Confidence in cumulative evidence

We will determine the quality of the statistically significant NMA findings using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach proposed by the GRADE Working group (2004) (52), and categorized as high, moderate, low, and very low quality evidence.

Limitation

As review authors are knowledgeable in the English language only, reviewing articles in other languages will be beyond the scope of this proposed analysis. Limitations due to the use of NMA, such as heterogeneity and inconsistency, are plausible in the proposed review if heterogeneity across RCTs introduces bias in the pairwise comparisons and there is incongruence between direct and indirect effect estimates, respectively (53).

Peer-review: Externally peer-reviewed.

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

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Supplement Link 1: <http://glns.co/oj7vl>

Supplement Link 2: <http://glns.co/yg6bx>

Supplement Link 3: <http://glns.co/89wuj>

What is your diagnosis?

A 30-year-old nulligravida woman presented to the gynaecology outpatient department, with the chief complaint of progressive, painless swelling in the perineal region for the last three months. The swelling was initially asymptomatic, but for the previous 15 days, it had started to protrude out on straining and caused difficulty during urination and defecation. There was no associated pain or fever. Her menstrual cycles were regular, and she had no dysmenorrhea, dyspareunia or chronic pelvic pain. On local examination, there was a boggy, non-tender swelling of 3x2 cm just inside the introitus, on the left side, located in the subcutaneous tissue of the labia majora, at the junction of upper two-thirds and lower one-third. The patient also complained of a similar swelling at the same site six months earlier, which was tense, painful and associated with fever. At that time, it ruptured spontaneously with the discharge of foul-smelling purulent fluid. A clinical diagnosis of Bartholin cyst was made, and the cyst was completely excised. Of note, the cyst had a thick wall and was densely adherent to the underlying structures. The bed was very vascular, leading to a blood loss of approximately 250 mL during excision, which was quite unusual for a Bartholin cyst. The post-operative period was uneventful. A one-month follow-up visit showed complete healing of the surgical scar, and the patient was symptom-free.

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Answer

Grossly, the cyst measured 3x2.5x2.5 cm, with wall thickness varying from 3-5 millimetres. The cavity was filled with solidified brownish material (Figure 1a). Microscopic evaluation confirmed the diagnosis of Bartholin cyst. The cyst wall was composed of fibro-muscular tissue lined by inflamed transitional epithelium. The normal Bartholin gland was seen in juxtaposition to the cyst wall (Figure 1b-d). However, in a few areas, the lining epithelium showed the presence of ciliated cells (Figure 1e,f), which is an extremely unusual finding and has been documented only once previously (1). Interestingly, the ciliated epithelium was negative for Periodic acid-Schiff (PAS) stain.

In contrast, the non-ciliated epithelium displayed a patchy magenta-coloured PAS-positive reaction, similar to the native glandular epithelium (Figure 1g-i). Multiple areas of the cyst wall were processed because of the resemblance of cavity contents to that of a chocolate cyst, which showed similar histo-morphology. There was no evidence of endometriotic cysts, such as endometrial gland or stroma, hemosiderin-laden macrophages or areas of haemorrhage.

Non-neoplastic cysts of the vulva and vagina can usually be easily diagnosed based upon the location, clinical features and subsequent histopathological characterisation of the lining epithelium (Table 1) (2,3). Although the literature regarding ciliated cysts is sparse, they are thought to arise due to Mullerian heterotopy, that is a Mullerian tissue that has been displaced from its original position during embryogenesis. These cysts are usually an incidental finding, but rarely can present as large masses distorting the normal anatomy. As the Mullerian tissue is sensitive to hormones, these cysts have a tendency to increase in size during pregnancy or due to exogenous hormone administration (2). They constitute a tight differential diagnosis in the present case. Clinically, a ciliated cyst can present as a cystic swelling in the postero-lateral aspect of the vulva (the specific location of a Bartholin cyst), and histopathology can also show ciliated lining epithelium (2,3). In the present case, a diagnosis of Bartholin cyst with ciliated/tubal metaplasia was favoured because of the presence of Bartholin glands and smooth muscle fibres in the cyst wall. The ciliated cyst of the vulva is described as being lined by ciliated, mucinous or non-mucinous columnar cells without smooth muscle cells in the cyst wall (4,5).



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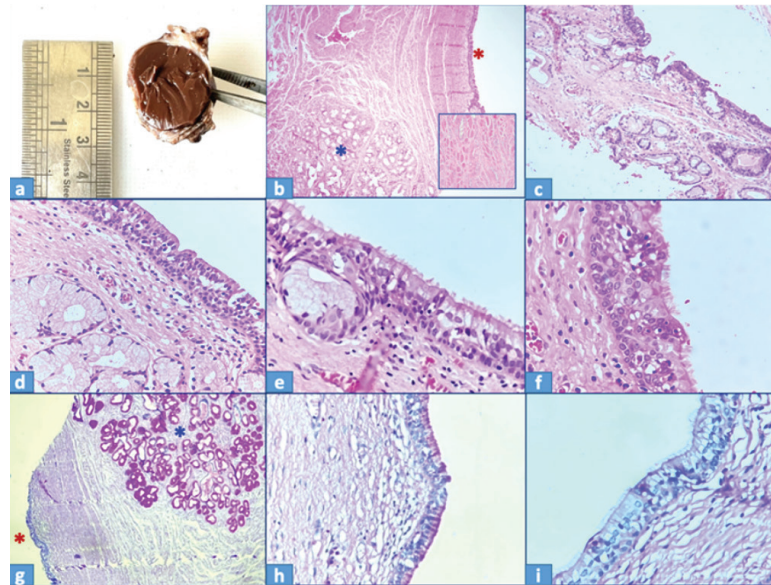


Figure 1. (a) Gross picture of the cyst showing solidified, chocolate-brown material in the cavity; (b) Cyst wall composed of fibromuscular tissue (inset) and native Bartholin gland (blue asterisk) and lined by transitional epithelium (red asterisk) [hematoxylin & eosin (H&E), x40]; (c) The lining epithelium of the cyst shows connection with the underlying glandular tissue (H&E, x100); (d, e) At places, the lining epithelium was pseudostratified to multi-layered with the presence of cilia (H&E, x400); (g) Intense Periodic acid-Schiff (PAS)-positive reaction noted in the native Bartholin gland (blue asterisk) but not in the lining epithelium (red asterisk) (PAS, x40); (h) Patchy PAS-positive reaction noted in the transitional epithelium (PAS, x100); (i) The ciliated epithelium is PAS-negative (PAS, x400)

Table 1. Diagnostic key points of non-neoplastic cystic lesions of vulvovaginal region (2,3)

S. no.	Entity	Usual location	Histopathology
1	Bartholin cyst	Posterolateral to the opening of vagina	- Cyst lining may be stratified squamous, transitional, mucinous (PAS, AB, mucicarmine positive) or flattened - Fibromuscular wall
2	Gartner’s cyst (mesonephric like cyst/ Wolffian duct like cyst)	Anterolateral wall of vagina lateral aspects of the vulva	- Lined by non-mucinous, non-ciliated cuboidal cells - Thin fibromuscular wall - Usually contains clear fluid
3	Epithelial inclusion cyst	Frequently seen on vulva as superficial lesions of varied dimensions	- Stratified squamous epithelial lining - Cavity contains keratinous material - May be associated with foreign-body reaction to keratin.
4	Mucous cysts	Usually are seen within the vestibule	- Mucus-secreting (PAS, AB, mucicarmine positive), cubo-columnar epithelial lining - Squamous metaplasia may be noted - No smooth muscle fibres in cyst wall
5	Ciliated cyst (Mullerian-type cyst)	Can be seen anywhere within vagina and vulva, although more common in the anterolateral wall	- The lining epithelium can be endocervical type (mucinous, columnar) or endometrial type (non-mucinous, columnar) or tubal type (ciliated, columnar) - No smooth muscle fibres in cyst wall
6	Cyst of canal of nuck (mesothelial cyst)	Found in inguinal canal or superior aspect of labia majora	- Lined by a single layer of flattened mesothelial cells
7	Endometriotic cyst	Usually seen in association with pelvic disease and can be seen anywhere in the vulvovaginal area.	- Any 2 of the following 3 findings: endometrial glands, stroma and hemosiderin laden macrophages.

PAS: Periodic acid-Schiff; AB: Alcian blue

The present case highlights that ciliated epithelium or tubal metaplasia can also be encountered in a Bartholin cyst. A definitive diagnosis can easily be achieved by clinical correlation, finding the acini of the Bartholin gland in the cyst wall and the presence of smooth muscle fibres. As various metaplasias are commonly encountered in the female genital tract, it is quite plausible that ciliated/tubal metaplasia in a Bartholin cyst is an under-reported entity rather than a very uncommon entity.

The authors certify that an appropriate patient consent form has been obtained.

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A fetus and its gestational sac out of the uterus: a tomography description of unscarred uterus rupture

To the Editor,

We recently became interested in possible maternal risks correlated with medical termination of pregnancy, for foetal anomaly, in the second trimester, at about 20 weeks. Stewart et al. (1), in their cases series, described different complications associated with second trimester pregnancy termination. However, we would like to also share our experience, considering the rarity and potentially severity of our case. Indeed, we reported an asymptomatic uterine rupture in an unscarred uterus, after medically induced termination of pregnancy with Mifepristone and Misoprostol (2). The case was notable for the absence of both symptoms and risk factors.

Our case concerned a 42-year-old pregnant woman, gravida three para two, without uterine scars. She came to our clinic for the first hospital attendance at 21 weeks and 5 days of gestational age. The foetal scan showed an intrauterine growth restriction associated with polyhydramnios and omphalocele. These findings raised the clinical suspicion of Edward's syndrome, and a subsequent amniocentesis confirmed trisomy 18. Therefore, after consultation the parents requested pregnancy termination. According to our internal protocol, a single dose of oral Mifepristone 600 mg was given. Twenty-four hours later, the patient took Misoprostol 100 mcg, administered every 6 hours and totalling four doses. After an entire cycle of therapy, the labour had not started, and the patient was asymptomatic. Moreover, painkillers were not administered.

Considering the absence of any response to therapy, to better clarify the situation, a combined trans-vaginal and trans-abdominal ultrasonography was performed. This examination raised the suggestion of uterine rupture. In particular, the uterine wall was not detectable around the gestational sac. However, the uterus was not clearly identifiable, and no free fluid was detected. Considering the soft and non-painful uterus

in a stable patient, tomography was performed to better define the situation. A posterior uterine wall rupture was detected, as reported in Figure 1. A 3D-reconstruction (Figure 2) of the rupture confirmed the clinical condition. Therefore, the patient underwent laparotomy (Figure 3) to allow pregnancy

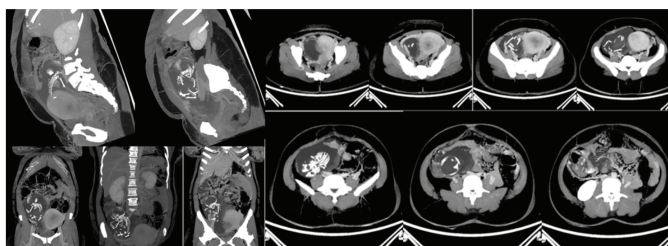


Figure 1. Tomography images of this case of uterine rupture

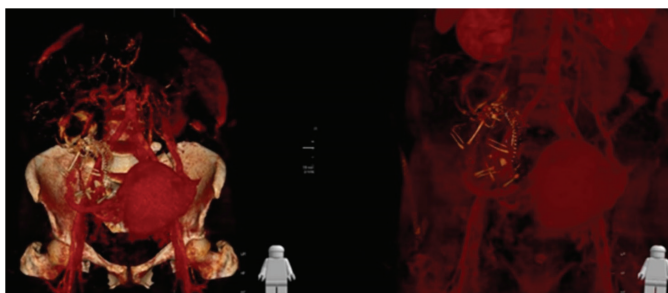


Figure 2. The 3D tomography reconstruction of the uterine rupture

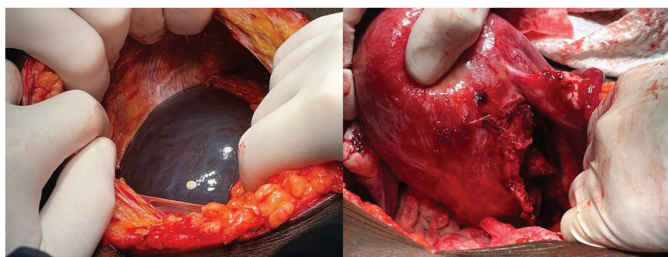


Figure 3. The surgical view: the amniotic sac outside the uterus and the uterine rupture

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termination and uterine reconstruction. Total bleeding was limited, and blood transfusion was not necessary. The patient was discharged well and without complications.

We believe that our experience could be educational and highlight the possible differential diagnosis of uterine rupture in cases of absence of response to medical induction of labour for pregnancy termination in the second trimester, even in patients without symptoms and risk factors.

Uterine rupture has been described in literature as a very rare, spontaneous complication in unscarred uteri (3-6), but even more rarely as an iatrogenic complication. This case draws attention to this very rare condition. In addition, we would like to draw the readers' attention to the performance ultrasound in this situation, which raised the possibility of uterine rupture, but was not definitively diagnostic (7). Clinical signs and symptoms are the true guide for this diagnosis but in our case these were absent, making the diagnosis even more challenging.

Furthermore, even if clinical findings are more important than imaging in cases of uterine rupture, we would like to share our tomography images, which could be of interest. Figure 1, 2 show the gestational sac, containing the foetus, out of the uterus, in an otherwise well patient, which is extremely rare, and rarely documented with imaging. However, we must emphasize that tomography is not indicated to routinely investigate the diagnosis of uterine rupture, even if it will clarify an unclear diagnosis in a stable and asymptomatic patient, when clinical findings and ultrasound are not conclusive.

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Third dose of COVID-19 vaccine: is there any place for it for pregnant women?

To the Editor,

Coronavirus disease-2019 (COVID-19) vaccination has been shown to be effective for COVID-19 primary prevention. Traditionally, two vaccine doses are required. There may be a decrease in immunity level after complete vaccination (1). Many scientists have proposed the use of an additional third dose vaccination when there is a new emerging variant and a possible decline in population immunity in general after standard mass vaccination. However, because the effectiveness of the third vaccine dose is unknown, any research into its efficacy is of interest. There are also numerous new ideas for using a new type of COVID-19 crossing to the previously fully vaccinated one. In many countries, the third dose of COVID-19 vaccine has been used to manage the emerging omicron variant of severe acute respiratory syndrome-coronavirus-2. It appears that those who received a less effective COVID-19 vaccine have insufficient immunity against the variant and require a booster. According to a recent study, a booster dose is effective in increasing immunity against the omicron variant (1). In this letter, the authors would like to discuss the specific situation for pregnant women.

COVID-19 vaccination is generally recommended for pregnant women. The vaccination can begin during the second trimester and be combined with other routine antenatal vaccinations (2). This study also found that a 12-week period or longer stimulated a good immune response after COVID-19 vaccination, and it can boost the immune level after the second dose of vaccine by about 1.2 times compared to the single first dose (2). It is currently unknown whether a third dose of COVID-19 plays a role in pregnant women with the current prevalence of the omicron variant.

There are numerous factors to consider. First, if pregnant women receive the first dose early, there is still time for the third dose of vaccine, which can be administered three months after the second dose. The second source of concern is the

predicted increase in the efficacy of the third dose vaccine. The level of protection after the second dose of vaccine has been reported to be between 86 and 90% (2). Using this data in a recently published predictive model for the expected efficacy of the third dose of COVID-19 vaccine, the expected protective efficacy after the third dose booster is 94% (2), leaving a gap of about 4-8% that the booster can stimulate increased immunity. Given that the COVID-19 vaccine has been proven safe and effective, there may still be a place for a third dose of COVID-19 vaccine for pregnant women if the vaccination schedule and pregnancy progression are compatible.

In the case of decreasing immunity, a third dosage of vaccine may be required. This exercise is likely to have a greater impact on third trimester pregnancies. COVID-19 can have a negative impact on pregnancy, especially if contracted during the third trimester. While a study is underway, results are not yet available. It is known that COVID-19 infection may raise the risk of premature birth, especially if contracted during the third trimester (3). Premature birth can result in a variety of difficulties for both the infant and the mother. Pregnant women who get COVID-19 in the third trimester are more likely to suffer serious disease, such as pneumonia and respiratory distress (3). This could result in more intensive medical procedures and difficulties for the mother. COVID-19 infection during pregnancy, particularly in the third trimester, may raise the risk of fetal discomfort, growth restriction, and stillbirth (3). However, it is crucial to highlight that these hazards are of low likelihood.

Finally, the decision to provide a third dose of the COVID-19 vaccine should be based on a comprehensive assessment of the existing scientific information, advice from health authorities, and consideration of the unique environment and demographic being targeted. It is best to follow the advice of healthcare professionals and public health officials who will constantly evaluate the benefits, dangers, and effectiveness

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of subsequent vaccine doses. When considering the use of a third dose, numerous aspects must be considered in order to determine its benefit-harm-effectiveness. A third dose may provide improved protection against COVID-19, particularly against developing variants, as well as potentially lowering the risk of severe illness, hospitalization, and death. The greater predicted protective efficacy of 94% indicates a significant benefit in terms of infection prevention and consequences. Nonetheless, any potential hazards or deleterious effects connected with a third dose must be considered. While COVID-19 vaccinations have generally shown a satisfactory safety profile, subsequent doses must be monitored on an ongoing basis to ensure their safety. The recognized negative effects of the vaccine should be balanced against the potential benefits. Finally, evaluating the effectiveness of implementing a third dosage entails taking into account aspects such as current vaccination coverage, the amount of community transmission, and the possible influence on virus propagation. It is critical to determine whether a third dose would make a meaningful difference in acquiring “herd immunity” or controlling the recent upsurge in the COVID-19 pandemic.

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Indocyanine green fluorescence imaging: an effective method to find inguinal sentinel lymph node in a case of vulvar carcinoma

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Abstract

The aim was to demonstrate that the technique of near infrared range/indocyanine green (NIR/ICG) could aid the detection of inguinal sentinel lymph nodes in patients with vulvar cancer, in addition to technetium-99m (Tc-99m) scanning. We present a case report of sentinel lymph node detection in a patient with vulvar cancer with two methods: Tc-99m scan and NIR/ICG. The video showed that bilateral inguinal lymph nodes were detected both by Tc gamma probe and NIR/ICG. NIR/ICG may be a safe and effective alternative method for identifying sentinel lymph nodes in cases of early-stage vulvar cancer, although more evidence is required. (J Turk Ger Gynecol Assoc 2023; 24: 291-2)

Keywords: Vulval carcinoma, indocyanine, radio tracer, sentinel lymph node

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Introduction

The aim of the case shown in the video article (Video 1) is to demonstrate that the technique of near infrared range/indocyanine green (NIR/ICG) may aid in the detection of inguinal sentinel lymph nodes in patients with vulvar cancer, as an addition to the accepted method of technetium-99m (Tc-99m) scanning. The method has been evaluated in a few studies (1,2), but the results are not always conclusive about the preferred method to highlight sentinel lymph nodes. Therefore, we present a case report of sentinel lymph node detection in a patient with vulvar cancer with Tc-99m and NIR/ICG.

Case description

The patient was a Caucasian woman, 67-years-old, who had non-insulin dependent diabetes. In her obstetrical history, there was one late abortion at 20 weeks and one vaginal delivery at term, complicated by foetal death during labour.

She required a gynaecological visit for the presence of a verrucous exophytic lesion of 25 mm close to right side of the posterior fourchette and an exophytic lesion of 7 mm on the left labia minora (Figure 1). A biopsy of the lesion described a squamous verrucous carcinoma, human papillomavirus-independent, with 0.2 mm of stromal invasion (stage Ia1). The patient underwent a positron emission tomography scan, which described only these two focal vulvar hypermetabolic areas. Therefore, the patient was scheduled for a simple vulvectomy. During the preoperative period the lesions demonstrated rapid growth and we opted to plan a right radical vulvectomy and a simple left vulvectomy, associated with sentinel lymph node detection. Tc-99m-labeled nanocolloid was injected at the four cardinal points of the lesion the day before surgery. A ICG solution was injected as the first surgical step, a few minutes before vulvar incision, around the lesion.



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Figure 1. Vulvar lesion

Bilateral inguinal lymph nodes were detected both by gamma probe and NIR/ICG (Figure 2, 3). After sentinel lymph node removal, vulvectomy was performed. The post-operative course was unremarkable.

The histopathologic diagnosis confirmed a grade 1 squamocellular vulvar carcinoma with no infiltration beyond the incisional margins to differentiate VIN. Bilateral inguinal lymph nodes were negative.

Conclusion

The mapping of sentinel lymph nodes may reduce surgery invasiveness in early-stage vulvar cancer and the use of a radioactive tracer is currently mandatory. Considering that this presented video demonstrated that inguinal lymph nodes were easily detected by both Tc-99m and NIR/ICG, we support the hypothesis that NIR/ICG may be a safe and effective alternative method for identifying sentinel lymph nodes in cases of early-stage vulvar cancer. The benefits of NIR/ICG include injection immediately prior to surgery and the absence of exposure to ionizing radiation. However, there isn't enough evidence of the equivalence of performance of the two methods and so further comparative studies are needed.

Video 1. <https://www.doi.org/10.4274/jtgga.galenos.2023.2023-4-11.video1>

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

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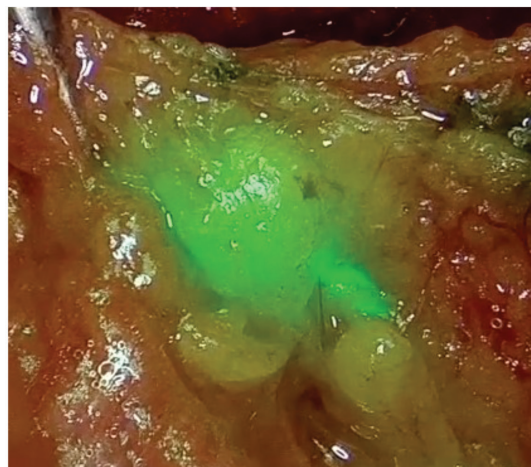


Figure 2. The sentinel lymph node identified by green indocyanine

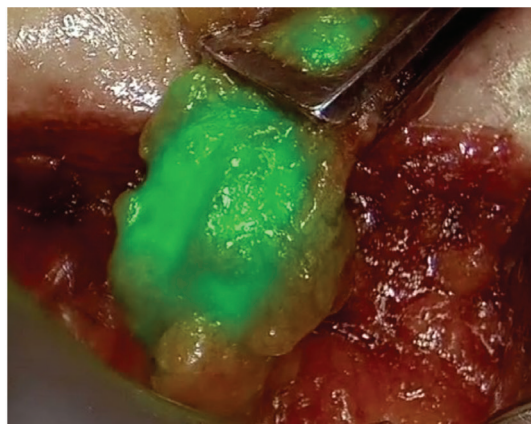


Figure 3. Sentinel lymph node removal, supported by the green indocyanine identification

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CONGRESS CALENDER

INTERNATIONAL MEETINGS

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

March 07-10, 2024	25 th European Congress on Gynaecological Oncology (ESGO), Barcelona, Spain
March 12-16, 2024	Society for Reproductive Investigation (SRI) 71 st Annual Scientific Meeting, Vancouver, Canada
April 18-20, 2024	10 th Congress of the Society of Endometriosis and Uterine Disorders (SEUD), Geneva, Switzerland
May 14-16, 2024	14 th European Congress on Menopause and Andropause, Florence, Tuscany, Italy
May 02-04, 2024	ASCCP 2024 Scientific Meeting, New Orleans, Louisiana, United States
May 17-19, 2024	American College of Obstetricians and Gynecologists (ACOG) 2024 Annual Clinical and Scientific Meeting, San Francisco, California, United States
May 18-22, 2024	American Society for Reproductive Immunology (ASRI) Annual Meeting 2024, Houston, Texas, United States
June 10-14, 2024	The Society of Obstetricians and Gynecologists of Canada Annual Clinical Scientific Conference, Edmonton, Canada
June 19-22, 2024	International Urogynecological Association (IUGA) 49 th Annual Meeting, Singapore
July 07-10, 2024	European Society of Human Reproduction and Embryology (ESHRE) 40 th Annual Meeting, Amsterdam, Netherlands
September 11-13, 2024	XXIX. European Congress of Perinatal Medicine, Vienna, Austria
October 06-09, 2024	34 th ISUOG World Congress, Dubai, UAE
October 16-18, 2024	International Gynecologic Cancer Society (IGCS) 2024 Meeting, Dublin, Ireland
October 19-23, 2024	American Society for Reproductive Medicine (ASRM) 80 th Annual Meeting, Denver, Colorado, United States
October 19-22, 2024	19 th World Congress on Menopause, Melbourne, Australia
October 27-30, 2024	ESGE 33 rd Annual Congress, Marseille, France
November 17-20, 2024	The 53 rd American Association of Gynecologic Laparoscopists (AAGL) Global Congress on Minimally Invasive Gynecologic Surgery (MIGS), New Orleans, Louisiana, United States
November 21-23, 2024	The 32 nd World Congress on Controversies in Obstetrics Gynecology & Infertility (COGI), Lisbon, Portugal

CONGRESS CALENDER

NATIONAL MEETINGS

(for detailed International Meeting please go website: <https://www.kongreuzmani.com/2024>)

February 02-03, 2024	Endometriosis and Adenomyosis - Bench to Bedside, İstanbul, Türkiye
February 29-March 03, 2024	CİSEF 4. Uluslararası Cinsel Sağlık Kongresi, KKTC
March 07-10, 2024	Uludağ Jinekolojik Endoskopi Kampı, Bursa, Türkiye
March 08-10, 2024	11. İstanbul Kadın Doğum Günleri, İstanbul, Türkiye
April 17-21, 2024	Kadın Sağlığı Dernekleri Federasyonu (KSDF) Kongresi, Antalya, Türkiye
May 15-19, 2024	21. Ulusal Jinekoloji ve Obstetrik Kongresi, K.K.T.C.
May 31-June 02, 2024	TAJEV Obstetrik ve Jinekolojide Güncel Yaklaşımlar Kongresi, İstanbul, Türkiye
September 06-08, 2024	3. Uluslararası Pelvik Taban ve Kozmetik Jinekoloji Kongresi, İstanbul, Türkiye
September 18-22, 2024	7. Minimal İnvaziv Jinekolojik Cerrahi Kongresi, İstanbul, Türkiye
October 02-06, 2024	6. Jinekoloji ve Obstetrikte Tartışmalı Konular Kongresi, Antalya, Türkiye
April 23-27, 2025	XV. Türk Alman Jinekoloji Kongresi, Antalya, Türkiye