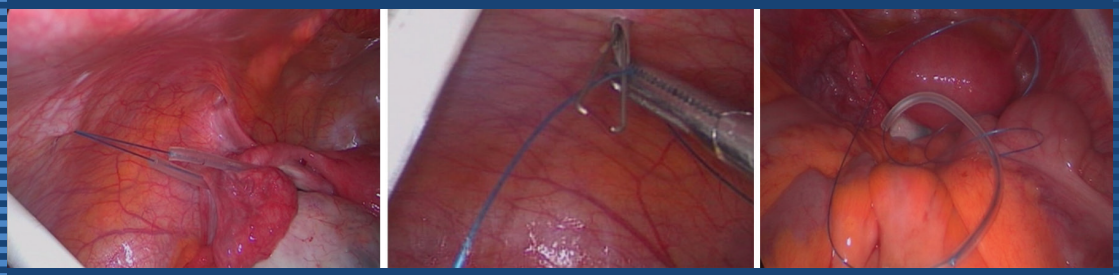
EISSN 1309-0380

Indexed in PubMed and Web of Science

TURKISH-GERMAN GYNECOLOGICAL EDUCATION and RESEARCH FOUNDATION

Journal of the Turkish-German Gynecological Association



Volume 23
Issue 2
June
2022

Cover Picture: Kobra Tahermanesh et al. Ovarian suspension loop

galenos yayınevi

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Online Publication Date: June 2022

E-ISSN: 1309-0380
International scientific journal published quarterly.

Journal of the
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Aims and Scope

Journal of the Turkish-German Gynecological Association is the official, open access publication of the Turkish-German Gynecological Education and Research Foundation and Turkish-German Gynecological Association and is published quarterly on March, June, September and December. The publication language of the journal is English. Manuscripts are reviewed in accordance with "double-blind peer review" process for both reviewers and authors.

The target audience of Journal of the Turkish-German Gynecological Association includes gynecologists and primary care physicians interested in gynecology practice. It publishes original works on all aspects of obstertrics and gynecology. The aim of Journal of the Turkish-German Gynecological Association is to publish high quality original research articles. In addition to research articles, reviews, editorials, letters to the editor, diagnostic puzzle are also published. Suggestions for new books are also welcomed. Journal of the Turkish-German Gynecological Association does not charge any fee for article submission or processing.

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

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Below the abstract provide 3 to 5 Keywords. Abbreviations should not be used as Keywords. Keywords should be picked from the Medical Subject Headings (MeSH) list (www.nlm.nih.gov/mesh/MBrowser.html).

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Ertan AK, Tanriverdi HA, Schmidt W. Doppler Sonography in Obstetrics. In: Kurjak A, Chervenak FA, editors. Ian Donald School Textbook of Ultrasound in Obstetrics and Gynecology. New Delhi, India: Jaypee Brothers; 2003. p. 395-421.

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Contents

Journal of the
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Editorial

Dear Colleagues,

It is my great pleasure to introduce the second issue of the "Journal of the Turkish-German Gynecological Association (J Turk Ger Gynecol Assoc)" in the publishing year of 2022. 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.

Laparoscopic myomectomy is a commonly used procedure in which the uterus is preserved. The power morcellation facilitates efficient breakdown and removal of tissues through small incisions. The use of power morcellation in laparoscopy may worsen survival rates in patients with malignancies. You will get the occasion to read an article from Germany reporting the outcomes of patients with early-stage uterine sarcoma after morcellation or total en-bloc resection, and evaluating potential signs of sarcoma preoperatively.

Diagnosis and management of patients with partial mole with a coexistent live fetus can be challenging. Most of the data we have is in the form of case reports. You will have the chance of reading a systematic review investigating the epidemiology, clinical presentation, and prenatal diagnosis of the cases with partial mole with a coexistent live fetus.

Dear Esteemed Reviewers,

Reviewing requires the investment of time and a certain skill set. Aczel et al. in Res Integr Peer Rev 2021;6:14 estimated that the total time that reviewers worked on peer reviews globally was over 100 million hours in 2020. We acknowledge your invaluable contribution to the progress of science. We are sincerely grateful to our reviewers who give their time to peer-review articles submitted to our journal.

Dear Participants,

I am very proud to say that the 14th Turkish-German Gynecology Congress was held in Antalya between May 28 and June 1 of 2022, with a great success with more than a thousand registered participants, 3 precongress courses, 1 live surgery session, 4 keynote lectures, 105 lectures, 5 satellite symposiums, 135 oral presentations, 126 poster presentations and 28 video presentations. It was a tremendous health education event for our community. We received many positive comments from the congress participants on the quality of the scientific presentations and the organization of the congress. Our success was in no small part due to experts such as you who could answer questions and disseminate information. I would like to thank all the participants once again for the time and dedication they gave to this event.

Please visit us online at www.jtgga.org and keep in touch with us by following us on Twitter @JtggaOfficial. I would like to wish you a happy and healthy summer 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

Marsupialization versus Word catheter in the treatment of Bartholin cyst or abscess: retrospective cohort study

Emine Karabük, Elif Ganime Aygün
Department of Obstetrics and Gynecology, Acıbadem University Faculty of Medicine, İstanbul, Turkey

Abstract

Objective: Bartholin cysts or abscesses are observed in approximately 2% of women, usually in their reproductive years. Although none of the treatments appear to be superior, there are several options including drainage with basic incision, Word catheter application, marsupialization, silver nitrate application, and excision. The primary outcome in this study was to evaluate the recurrence rates in patients who underwent marsupialization or Word catheter for the treatment of Bartholin cyst or abscesses, and the secondary outcome was to evaluate the rates of patient satisfaction.

Material and Methods: A total of 196 patients who underwent either Word catheterization or marsupialization for the treatment of Bartholin cyst or abscesses between 2014 and 2017 were included in this retrospective cohort study. The size and location of the cyst/abscess, the operation duration, and the recurrence was recorded. A 5-point visual analog scale (VAS) was used to assess patient satisfaction and whether patients would recommend thier treatment to others.

Results: Recurrence was observed in 11 (8.3%) patients in the marsupialization group, and 12 (18.8%) patients in the Word catheter group ($p=0.034$). Median (range) VAS scores in the marsupialization group were better than the Word catheter group [4 (1-5) vs 3 (1-5); $p<0.001$].

Conclusion: Higher recurrence rate and dissatisfaction level were found in the Word catheter group. The only advantage of using Word catheter was its short operation time. These results appear to show that marsupialization should be the first-line treatment for Bartholin cysts and abscesses. However, the small number of cases and the retrospective nature of this study mean that larger, prospective studies are required to support this hypothesis. (J Turk Ger Gynecol Assoc 2022; 23: 71-4)

Keywords: Bartholin abscess, Bartholin cyst, recurrence, patient satisfaction

Received: 26 January, 2022 **Accepted:** 20 March, 2022

Introduction

Bartholin cyst is a swelling resulting from mucus build-up located at the 4- and 8-o'clock positions of the vulvar vestibule. If the same swelling is accompanied by signs of infection or inflammation such as redness, swelling, hotness, and tenderness, it is described as an abscess (1). Bartholin cysts or abscess are observed in around 2% of women, generally in their reproductive period (2). Several management options are available for Bartholin cysts, including drainage with basic incision, Word catheter, marsupialization, silver nitrate application or excision (3). In the marsupialization procedure, to provide drainage from the glands and to prevent scar formation, a 1.5-3 cm long incision is made in the cyst/abscess. After performing drainage to prevent the closure or formation of a new cyst, the cyst capsule is sutured to the edge, which is fixed to the outer side, and re-epithelialization ultimately occurs (4). Local, regional or general anesthesia is required during the marsupialization procedure.

An alternative treatment is the Word catherter. The Word catheter is a 5.5 cm long, 15-French silicone device with a 3 cm long balloon, which is placed in the cyst or abscess to provide canal drainage and epithelialization. This procedure eliminates the requirement for an operation (2). It can be performed as

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DOI: 10.4274/jtgga.galenos.2022.2022-1-6

a day case. However, its location should not change while providing drainage for approximately 4 to 6 weeks. (2). In the literature, the recurrence rates reported for both approaches are very variable. While the recurrence rate is 2-25% for marsupilization, this rate is between 3% and 17% for a Word catheter (2,3).

Objective

The aim of this study was to compare the results obtained from the patients who underwent marsupialization or Word catheter due to Bartholin cyst or abscesses. The primary outcome of the study was to compare the recurrence rates, and the secondary outcome was to compare the satisfaction levels of the patients.

Material and Methods

In this retrospective cohort study, all patients were included who underwent marsupialization or Word catheter for Bartholin cyst or abscess in our hospitals between 2016 and 2021. The study design was approved by the Acıbadem Mehmet Ali Aydınlar University Ethics Committee (approval number: 2021-20/28).

Patients data were extracted from health records, including contact information. Clinical data included the size of the Bartholin cysts or abscesses, their location, operation duration, and the presence or absence of recurrence. Identified patients were asked how satisfied they were the treatment and whether they would recommend this treatment to others via survey. The responses were recorded.

Exclusion criteria were patients without current contact information and patients undergoing any other treatment for Bartholin cyst or abscess, other than marsupialization or Word catheter.

For marsupialization, the patient was placed in the lithotomy position and 2% lidocaine was infiltrated to the skin lateral to hymen. The stabilization of the cyst manually followed by the opening of the cyst wall with a vertical incision about 1.5-2 cm long. The cyst was drained of its contents, cyst membrane was everted, and the cavity was washed with saline. The cyst wall was everted to the skin edge with 2-0 absorbable suture (polyglactin 910).

In the Word catheter procedure, the infiltration of 2% lidocaine was followed by a 5 mm incision. The contents of the cyst or abscess were cleaned out. Then the Word catheter (Cook Medical Inc, Bloomington, IN, USA) was placed, after being inflated with 3 mL saline solution, and one suture was placed. It was kept stationary for 4 weeks.

All patients were interviewed about their overall discomfort levels, evaluated using a 5-point visual analog scale (VAS). The categories were: 1, poor/very difficult; 2, sufficient/moderately difficult; 3, medium/average difficulty; 4, good/easy; and 5, excellent/very easy. Finally, patients were asked if they would recommend their surgery type to other patients undergoing the same procedure.

Statistical analysis

SPSS, version 25.0 (SPSS, Chicago, IL, USA) was used for analysis. Continuous variables were expressed as mean ± standard deviation, median (range), whereas categorical variables were expressed as percentages and frequencies. The Shapiro-Wilk test was used to assess the equality of variance of the data. Chi-squared and Fisher's exact tests were used for categorical variables, t-test to compare independent variables with normal distribution, and Mann-Whitney U test to compare independent variables with abnormal distribution. Kaplan-Meier curves were constructed to present the time to recurrence of the cyst or abscess and log-rank test was used to test differences in time to recurrence. Statistical significance was assumed when $p \leq 0.05$.

Results

A total of 196 patients were included, of whom 132 (67.3%) underwent marsupialization and 64 (32.7%) underwent Word catheterization. The mean age of the patients was 37.29±10.37 in the marsupialization group and 36.10±11.26 in the Word catheter group (p=0.297). Basic demographic data of the two

Table 1. Demographic data of the groups

	Marsupialization (n=132)	Word catheter (n=64)	p
Gravida*	2 (0-5)	2 (1-5)	0.675
Parity*	2 (0-4)	2 (1-4)	0.069
Age (years)*	37.29±10.37	36.10±11.26	0.297
Body mass index (kg/m²)*	24.4±3.9	23.8±3.2	0.394
Menopause (+), (%)	22 (16.7)	8 (12.5)	0.447
*Menopause length (years) n	3.39±3.40	5.6±8.53	0.544
Chronic disease (+) n, (%)	19 (14.4)	4 (6.31)	0.129
Previous operation (+) n, (%)	26 (19.7)	21 (32.8)	0.078
*Values are given as mean ± standard deviation or median (minimum-maximum)			

groups were compared in Table 1. There was no significant difference between the groups in terms of demographic features.

Bartholin cysts were present in 104 (78.8%) and abscess in 28 (21.2%) of the patients in the marsupialization group while cyst in 47 (73.4%) patients and abscess in 17 patients (26.6%) in the Word catheter group (p=0.404).

While 60 (45.5%) of the cyst-abscesses in the marsupialization group were on the right and 2 (1.5%) were bilateral, in the Word catheter group 24 (37.5%) were on the right and 2 (3.1%) were bilateral. The mean cyst-abscess size was 3.66±1.21 cm in the marsupialization group and 3.65±0.73 cm in the Word catheter group. The location and size of the cysts were similar between the two groups (p=0.473 and p=0.146, respectively).

The mean operation time was significantly shorter in the Word catheter group (15.85±2.88 min), compared to the marsupialization group (21.67±4.87 min) (p=0.001). Postoperative complications was observed in 7 (5.3%) patients in the marsupialization group and 2 (3.1%) patients in the Word catheter group (p=0.495). All of the complications were postoperative infection.

A total of 11 patients (8.3%) in the marsupialization group and 12 patients in the Word catheter group (18.8%) had recurrence (p=0.034). The recurrence interval was 7.27±6.46 months for the marsupialization group and 5.58±3.34 months for the Word catheter group. The time interval to recurrence of the groups after the operation is shown in Figure 1 (log-rank test, p=0.543). Ten patients with recurrence in the marsupialization group were treated with cystectomy and 1 patient with antibiotics. Nine patients with recurrence in the Word catheter group underwent cystectomy and 3 had antibiotic treatment (p=0.660).

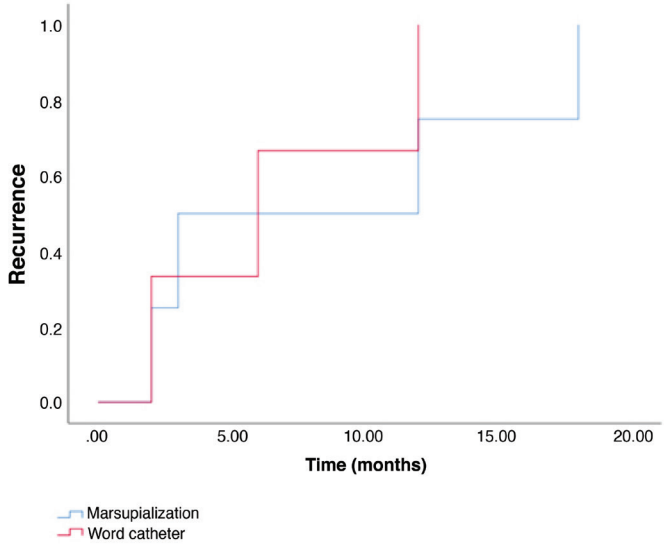

Figure 1. Kaplan-Meier curve for time to recurrence of the Bartholin cyst or abscess after treatment

The patient satisfaction was assessed with the postoperative VAS scale. The median (range) VAS scores (score: 4 minimum: 1, maximum: 5) in the marsupialization group were 4 (1-5) and were significantly better than those reported by patients in the Word catheter group with a median (range) score of 3 (1-5) (p<0.001). When patients were asked if they would recommend this surgical procedure to other patients, 12 (9.1%) patients in the marsupialization group and 13 (20.3%) patients in the Word catheter group responded negatively (p=0.027). In the marsupialization group, dissatisfaction was caused in 4 out of 12 (33.3%) by recurrence and in 8 out of 12 (66.7%) by pain. In the Word catheter group, the causes of dissatisfaction were length of treatment in 8 (61.5%), recurrence in 4 (30.8%) and pain in 1 (7.7%) (p=0.001).

Discussion

In this retrospective cohort study, marsupialization and Word catheter treatments for Bartholin cyst or abscesses were compared. Our primary outcome was to compare the recurrence rates. Similar to the reported literature, the recurrence rate was 8.3% in the marsupialization group and 18.8% in the Word catheter group. Although the recurrence rates, and the pain scores were investigated and the average treatment cost was evaluated in previous studies there has not been any current study which compares the patients' comfort and satisfaction (5-7).

Treatment of the Bartholin cyst or abscess also depends upon the symptoms. There are many treatment options, including medical treatment, simple drainage, destruction with silver nitrate or alcohol, Word catheter, marsupialization, and excision of the gland. Asymptomatic and small Bartholin cysts may not need any treatment, while large symptomatic cysts and abscesses need to be treated with surgical intervention.

Incision and drainage is a simple and quick method of providing relief. However, this method is prone to recurrence of cyst or abscess formation (8). The most important issue in the selection of treatment methods is the recurrence rate and it differs by the initial type of management.

Recurrence rates are not very clear in the literature. Recurrence rates for Bartholin duct cysts or gland abscesses after Word catheter compared with marsupialization are reported to range from 2% to 17% and 3% to 25%, respectively (2,9).

Kroese et al. (5) found that the pain scores were higher for the Word catheter compared to marsupialization and they did not observe significant difference in the recurrence rates. Reif et al. (6) suggested that Word catheter has acceptable recurrence rates and it is a low-cost procedure. However, we detected noticeably higher patient satisfaction in the marsupialization group in our study.

The secondary outcome was to compare the satisfaction levels of the patients. When they were asked whether they would recommend this surgical application to other patients, there was a significant difference in satisfaction with patients in the Word catheter group being more dissatisfied. The main reason for this was the length of the treatment and the high rate of the recurrence.

Conclusion

In conclusion, recurrence rate and patient dissatisfaction were greater in the Word catheter group. The only advantage of the Word catheter application was its short operation time, which only differed by a median of around eight minutes. Thus we suggest that marsupialization should be the first-line treatment for Bartholin cysts or abscesses.

Ethical Committee Approval: *Before the study, the approval form was taken from the Local Ethics Committee of Acıbadem Mehmet Ali Aydınlar University (approval number: 2021-20/28).*

Informed Consent: *It was obtained from all participants.*

Peer-review: *Externally peer-reviewed.*

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

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

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

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Effect of tumor morcellation in patients with early uterine sarcoma: a multicenter study in Germany

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Abstract

Objective: The use of power morcellation at laparoscopy may worsen survival rates for patients with malignancy. The aim of the present study was to report the outcome of patients with early-stage uterine sarcoma after morcellation or total en-bloc resection, and evaluate potential signs of sarcoma preoperatively.

Material and Methods: This multicenter retrospective study consisted of patients, who underwent surgery for FIGO-stage-1 uterine sarcoma. Twenty-four patients were divided into a non-morcellation group and a morcellation group. Clinical records and the outcomes of patients, including one-, three- and five-year survival rates were reviewed. Preoperative characteristics of patients with sarcoma were compared to those of a control group with uterine myoma (1:4 ratio), matched by age and type of operation.

Results: Obesity was an independent risk factor for uterine myoma. Tumor growth, solitary growth, largest-diameter lesion >8.0 cm, and anechoic areas suggesting necrosis and increased vascularization were significantly more common in the sarcoma group. A large tumor diameter was significantly associated with mortality. Patients in the non-morcellation group had a slightly lower disease-free survival, but poorer overall survival (OS) rates compared to patients in the morcellation group, but neither difference was statistically significant. Patients in the non-morcellation group, who had undergone a re-exploration experienced late recurrence, but no upstaging was evident after the operation.

Conclusion: Preoperative ultrasound characteristics could be useful to distinguish sarcoma from leiomyoma of uterus. Morcellation of a sarcoma may increase abdominal and pelvic recurrence rates, but may not be associated with OS in patients with FIGO-stage-1 disease. (J Turk Ger Gynecol Assoc 2022; 23: 75-82)

Keywords: Morcellation, unexpected malignancy, sarcoma, laparoscopy, survival rate

Received: 29 September, 2021 **Accepted:** 25 January, 2022

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Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2022.2021.9-17

Introduction

Uterine sarcomas are rare malignancies that arise from the connective tissue or smooth muscle of the uterus, accounting for 1-2% of all malignancies of the uterus and less than 1% of all genital malignancies (1).

The prognosis or diagnosis of uterine sarcomas are rendered difficult by their rarity. Existing imaging techniques do not permit the differentiation of leiomyosarcoma (LMS) from myoma, preoperatively (2). A preoperative biopsy is obsolete because of the risk of tumor dissemination. Moreover, a sarcoma is not diagnosed easily during surgery because a frozen-section analysis or cytological investigation does not permit the differentiation of sarcoma from myoma (2). Thus, sarcomas tend to remain underdiagnosed and are usually treated by myomectomy or hysterectomy using morcellation techniques.

Minimally invasive surgery (MIS) is associated with lower surgical morbidity than laparotomy, but both methods have similar disease-related outcomes in patients with endometrial cancer (3-6). Despite the established advantages of MIS and the use of electromechanical morcellators (EMM), the morcellation of unexpected sarcomas during surgery has been known to cause the dissemination of tumor tissue, resulting in poor survival outcomes (7).

For patients undergoing myomectomy or hysterectomy, there was a warning, in April 2014, against the use of laparoscopic power morcellation by the FDA (8). Unexpected malignancy was estimated to occur in 1 out of 350 women (8-11). After this warning, several renowned hospitals across the world stopped using EMM.

The purpose of this multicenter analysis was to estimate the influence of morcellation on clinical outcomes in patients with early-stage uterine sarcomas (FIGO-stage-1) in Germany. Furthermore, we estimated risk factors for the presence of uterine sarcoma and analyzed preoperative ultrasound characteristics in order to determine signs of sarcoma preoperatively.

Material and Methods

A retrospective multicenter study was performed at four departments of obstetrics and gynecology in Germany from June 2007 to May 2019. The study was approved by the Ethical Committee of the Medical Faculty of the University of Luebeck (approval number: 18-115). The information system of the academic teaching hospitals of Klinikum Leverkusen, Vivantes Humboldt, the University Hospital of Luebeck, and the University Hospital of Kiel were used by the authors to identify women who had undergone surgery for FIGO-stage-1A or 1B uterine sarcoma (12). Patients with carcinosarcoma and those who had been treated with endoscopic retrieval bags were also excluded.

The data of 24 patients were collected. Indications for the intervention, medical history, body mass index (BMI) and preoperative symptoms, histological results, and postoperative data were analyzed. Pathological slides were reviewed by two experienced pathologists. A clinical follow-up examination was performed every three months for all patients.

Tumor recurrence, disease-free survival (DFS), anatomical location of tumor recurrence and overall survival (OS) were recorded during follow-up examinations. Patients were divided into the following two groups: those who underwent total laparoscopic, abdominal or vaginal hysterectomy without morcellation (non-morcellation group), and those who underwent hysterectomy or myomectomy including vaginal, laparoscopic or abdominal, morcellation (morcellation group).

A group of patients with uterine myoma selected from all of those who underwent hysterectomy or myomectomy were matched by age and type of operation (4:1 ratio) during the same period. Patient characteristics and the indication for surgery were analyzed. Preoperatively, all patients were examined by experienced gynecologists on the basis of German guidelines (13). Preoperative ultrasound parameters (14), such as size of the tumor, anechoic areas suggesting necrosis (Figure 1), solitary growth, increased vascularization (Figure 2), an irregular lining, and endometrial thickness >5 mm in postmenopausal patients were taken into account. Ultrasound was performed within four weeks before surgery, and ultrasound characteristics of patients with uterine sarcoma were compared with those of controls with uterine myoma.

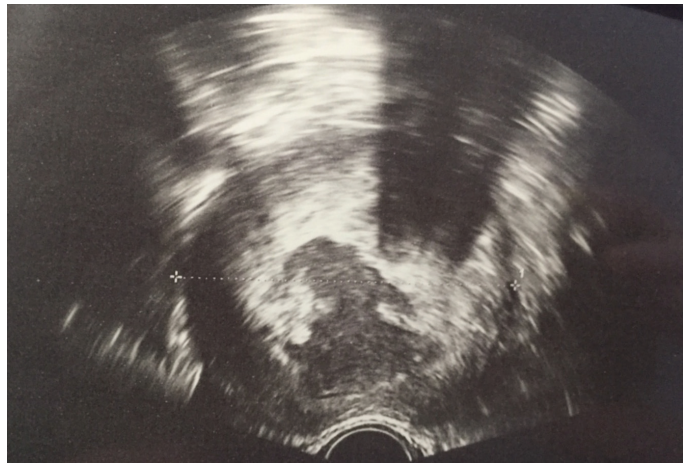

Figure 1. Transvaginal ultrasound showing the sagittal diameter of the fundus of the uterus and the size of the tumor. Inhomogeneous appearance, central hypoechoic area, degenerative cystic changes atypical for myoma suggesting necrosis

Statistical analysis

Data were collected in an Excel 2010 table (Microsoft Corporation, Redmond, WA, USA) and evaluated using SPSS software, Version 26 (IBM Inc., Armonk, NY, USA). To compare absolute and relative frequencies of clinical parameters, either a chi-square-test or a Fisher's exact test was performed, depending on scaling and distribution of the variables. A p-value <0.05 was considered statistically significant.

Results

The patients' characteristics were summarized in Table 1. The youngest woman was 40 years old and the oldest one was 84 years old. The mean weight of the uterus was 324.1 grams.

The most common indication for surgery was bleeding disorders (62.5%); the percentages of indications for surgical procedures are shown in Table 2. The types of operation in each department are summarized in Table 3. The majority of unexpected sarcomas (7/10) were diagnosed after performing laparoscopic supracervical hysterectomy (LASH).

One patient had used tamoxifen and another patient had undergone irradiation of the pelvis. Seven patients had a family history of cancer (29.1%), and one patient had a family history of sarcoma (4.2%). The principal characteristics of patients with sarcoma are summarized in Table 1. Seven patients underwent dilatation and curettage preoperatively. The diagnostic success rate was 71.4%; the outcome of the histological investigation was false negative in two cases.

Manual morcellation was applied in two patients who underwent laparoscopic hysterectomy as the initial procedure, while power morcellation was performed in eight patients who underwent laparoscopic myomectomy or subtotal hysterectomy as the initial procedure. In the morcellation group, five patients underwent a staging laparotomy and two a staging laparoscopy with cytological examination of fluid from the pouch of Douglas, bilateral ovariectomy, removal of the cervical stump, omentectomy, and multiple peritoneal biopsies two to four weeks after the first procedure. In the non-morcellation group, only two patients underwent a staging operation. Two patients underwent a pelvic and para-aortic lymphadenectomy; no lymph node metastasis was found. A computed tomography scan of the pelvis and the chest was performed in all patients, either preoperatively or postoperatively. The staging operations and examinations did not reveal upstaging of the tumor. Subsequent treatment, the results of follow-up, and the relapse of sarcoma are shown in Table 1 and Figure 3. Four patients (16.7%) underwent a third operation at which a complete resection was performed. Four out of six patients with distant recurrence developed a metastasis in the lung.

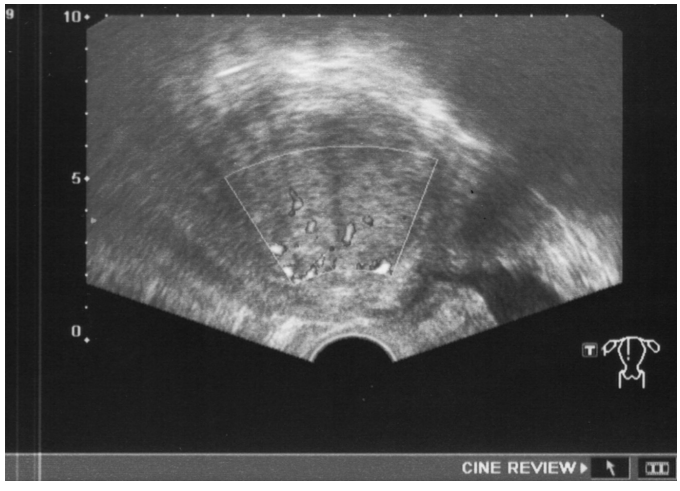

Figure 2. Transvaginal color Doppler ultrasound shows increased central vascularization in the heterogeneous tumor (transverse orientation of the ultrasound probe)

The mean age (± standard deviation) of controls (55.3±10.51 years) and the types of operations were similar (Table 4). Twelve women in the sarcoma group (50.0%) were postmenopausal, and 47 (49%) of the uterine myoma group. The average BMI of controls was 29.8 kg/m^2. In contrast to women with sarcoma, a BMI of 25 kg/m^2 was an independent risk factor for uterine myoma ($p<0.05$). The most common indications for surgery and potential ultrasound characteristics are shown in Table 4. The median diameter of the tumors was 5.6 cm. A large tumor diameter ($p<0.05$) and higher tumor stage (FIGO-1B) were significantly associated with mortality rates ($p<0.05$).

Discussion

We compared the outcomes of FIGO-stage-1 uterine sarcoma after morcellation versus hysterectomy without morcellation. Our results revealed a slightly better DFS for the non-morcellation group compared to the morcellation group, but with no benefit in OS. However, neither difference was statistically significant.

Obesity (BMI >25 kg/m^2) was not significantly predictive of uterine sarcoma, which is in contrast to the general view of obesity as a risk factor for malignancies, and was also in contrast to the opposite trend for patients with uterine myoma. In a study comprising 31 patients with uterine sarcoma, Cho et al. (15) found a BMI ≤20 kg/m^2 to be an independent risk factor for disease. Obesity is known to be a major risk factor for breast cancer (hormone receptor positive) and endometrial cancer (type 1 endometrioid tumor) (16). Moreover, obesity is also a major risk factor for uterine myoma, which is typically an estrogen-dependent tumor (17). Pathophysiological differences between endometrial cancer, uterine myoma, and uterine sarcoma may explain the lower BMI in women with uterine sarcoma.

In accordance with published data (18), uterine bleeding and abdominal pain were almost equally common in patients with uterine sarcoma and those with uterine myoma in our study. However, tumor growth as an indication for surgery was significantly more common in the sarcoma group, which might explain the largest diameter of tumor in sarcomas group. Radiation exposure and a history of radiation therapy of the pelvis have all been reported to increase the likelihood of developing sarcoma; the same has been noted in breast cancer patients treated with tamoxifen (19). However, in the present study only one patient had a history of radiotherapy and, also, one patient had undergone treatment with tamoxifen.

In our analysis 13 of 24 cases had abnormal uterine bleeding, however we performed dilatation and curettage preoperatively only in seven of them. The diagnostic success rate was 71.4%; false-negative results of histology were noted in two cases. Similar data were reported in a large review of 302 sarcomas by Wais et al. (20) in which uterine sarcoma was diagnosed

Table 1. Patient characteristics, adjuvant management and survival outcome

	n	Non-morcellation group	Morcellation group	Total	p
Age (years)	24	52.8±15.48	62.7±12.48	58.6±14.89	**0.074**
BMI (kg/m^2)	22	29.12±7.81	24.17±2.51	26.87±6.40	**0.159**
Menopause status					
Premenopausal	24	3 (21.4%)	6 (60.0 %)	9 (37.5%)	**0.092**
Perimenopausal	24	2 (14.3%)	1 (10.0 %)	3 (12.5%)	**0.629**
Postmenopausal	24	9 (64.3%)	3 (30.0 %)	12 (50.0%)	**0.098**
Tumor size >8 cm	22	8 (61.5%)	4 (44.4%)	12 (54.5%)	**0.666**
Abnormal bleeding	24	8 (57.1%)	7 (70.0%)	13 (54.2%)	**0.697**
High vascularisation	23	5 (35.7%)	3 (33.3%)	8 (34.8%)	**0.633**
LMS	24	8 (57.1%)	8 (80.0%)	16 (66.7%)	**0.388**
ESS	22	6 (50.0%)	2 (20.0%)	8 (36.4%)	**0.204**
Grading	19	-	-	-	**0.524**
1	-	7 (50.0%)	3 (60.0%)	10 (52.6%)	-
2	-	3 (21.4%)	0	3 (15.8%)	-
3	-	4 (28.6%)	2 (40.0%)	6 (31.6%)	-
FIGO	20	-	-	-	**0.639**
IA	-	4 (40.0%)	3 (30.0%)	7 (35.0%)	-
IB	-	6 (60.0%)	7 (70.0%)	13 (65.0%)	-
Upstaging	20	0	0	0	-
Chemotherapy	23	1 (7.1%)	1 (11.1%)	2 (8.7%)	**0.640**
Therapy with gestagene	24	0	2 (20.0%)	2 (8.3%)	**0.163**
Recurrence	24	5 (35.7%)	5 (50.0%)	10 (41.7%)	**0.678**
Location of recurrence					
- Abdomen/pelvis	-	3	1	3	-
- Distant (bone, lungs, liver, kidney)	-	1	3	4	-
- Both	-	1	1	2	-
DFS 1 year	23	70%	78.6%	75.5%	**0.537**
DFS 3 years	21	56%	61.5%	59.0%	**0.623**
DFS 5 years	15	29%	37.5%	33.3%	**0.573**
OS 1 year	23	100%	92.9%	95.8%	**0.565**
OS 3 years	18	87.5%	80%	85.7%	**0.588**
OS 5 years	12	80%	71.4%	72.7%	**0.636**
DFS 1 year					
- After reoperation	-	0%	-	-	-
- Without reoperation	-	100%	-	-	-

BMI: Body mass index, LMS: Leiomyosarcoma, ESS: endometrial stromal sarcoma, DFS: Disease free survival, OS: Overall survival, ESS: Endometrial stromal sarcoma

in 65% of patients, who underwent endometrial sampling preoperatively. Another analysis demonstrated a misdiagnosis rate of 19% for endometrial cancer and 36% for sarcoma (21). However, abnormal uterine bleeding remains a significant clinical sign and should not be underestimated. We encourage the use of endometrial sampling in patients with suspicious myoma, especially in the presence of abnormal uterine bleeding.

Solitary tumors larger than 8 cm in size with intensified peripheral and central vascularization were the most common features of uterine sarcoma on ultrasound (14,22). According to Exacoustos et al. (14) ultrasound features, such as single lesions, increased central and peripheral vascularity, large-diameter lesions (≥8 cm), and cystic degeneration, were significantly associated with uterine sarcoma. Viewing these features together, the authors registered a sensitivity of 100% and a specificity of 86%. However, the small sample size of the study (8 patients with sarcoma compared with 225 patients with leiomyoma) was a limitation to come to a robust conclusion. We compared ultrasound features between 24 uterine sarcomas and 96 uterine myomas, and observed the following ultrasound features predictive of uterine sarcoma: solitary growth, largest-diameter lesion >8.0 cm, anechoic areas suggesting necrosis, and increased vascularization. However, we observed anechoic areas suggestive of necrosis in a mere 20.8% of our cases, and high vascularization in 34.8%.

Table 2. Indications for surgery

Indications for abdominal-vaginal hysterectomy, TLH, LASH, and myomectomy	Patients who underwent surgery n (%)
Bleeding disorders	13 (54.1)
Uterine growth	10 (41.6)
Histological diagnosis of sarcoma with D&C	5 (20.8)
Abdominal pain	5 (20.8)
Urinary disorders (incontinence or obstruction)	3 (12.5)
TLH: Total laparoscopic hysterectomy, LASH: Laparoscopic supracervical hysterectomy D&C: Dilatation and curettage	

Table 3. Type of operations and their percentages

Type of operation	LASH	TLH	LM	VH	TAH	AM
Patients with sarcoma (n, %)						
Leverkusen Municipal Hospital	3	1	0	2	3	0
University Hospital of Luebeck	2	1	1	0	2	1
University Hospital of Kiel	2	1	0	0	2	0
Vivantes Humboldt, Berlin	0	2	0	0	1	0
Multicenter analysis	7	5	1	2	8	1
Preoperatively known sarcoma	0	2	0	0	3	0
Unexpected sarcoma without morcellation	0	2	0	2	5	0
Morcellated sarcoma	7	1	1	0	0	1
LASH: Laparoscopic supracervical hysterectomy, TLH: Total laparoscopic hysterectomy, LM: Laparoscopic myomectomy, VH: Vaginal hysterectomy, TAH: Total abdominal hysterectomy, AM: Abdominal myomectomy						

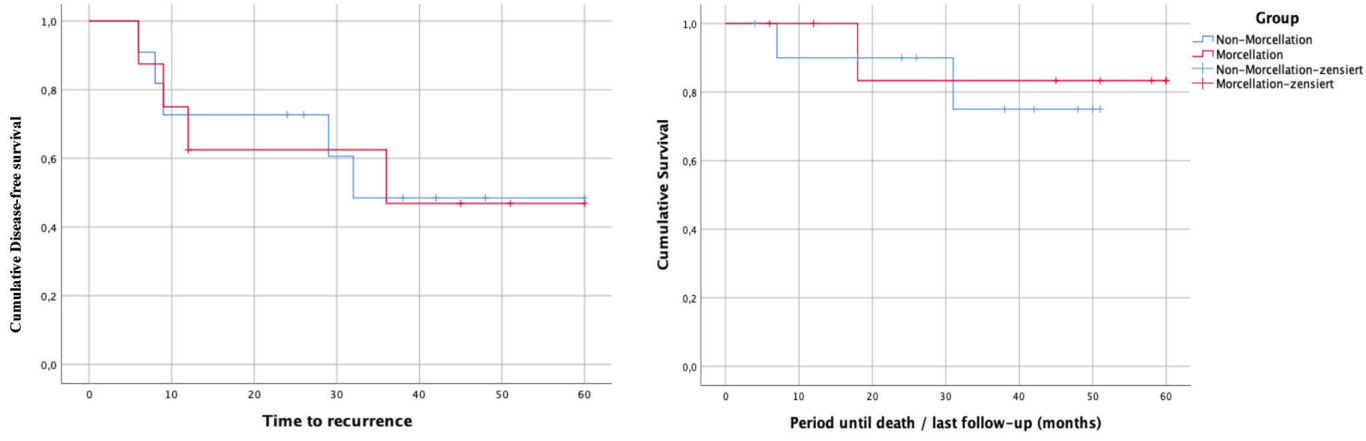

Figure 3. Oncologic outcome of 24 patients with apparently early uterine sarcoma in relation with tumor morcellation (overall survival at the right and disease-free survival at the left)

A greater frequency of sarcomas was noted in the presence of characteristics such as a solitary tumor (73.9%) and tumor size larger than 8 cm (54.5%). Uterine sarcomas are not easily identified.

Tumor size is known to be a prognostic factor for early LMS (23). In the present study, the tumor size was significantly associated with mortality rates. A higher tumor stage (FIGO-1B) was also significantly associated with the outcome. In a study comprising 34 patients with early LMS, Lin et al. (24) evaluated the effect of morcellation on the outcome and concluded that the size of tumor outweighed morcellation; the former was more significant than morcellation in predicting a poor outcome. However, it should be noted that, in small studies, a slight difference in tumor size might cause a large difference in the combined statistical analysis of survival outcome.

In unexpected uterine sarcomas the use of morcellators has been reported to result in cancer upstaging and worsen survival rates (25). However, we reported no upstaging of the tumor in 10 patients who underwent staging operations at two to four weeks after the initial procedure. Our results concur with the data reported by Park et al. (26), who performed complete staging surgery in 23.9% of their patients and observed no upstaging in any patient. In contrast, Einstein et al. (27) mention that approximately 15% of patients were upstaged by re-exploration, particularly those with LMS who underwent EMM. Even in a large systematic review (28), the authors were unable to conclude whether morcellation of sarcomas causes upstaging of cancer compared to *en bloc* removal. Different morcellation techniques could be the reason for the varying incidence of intra-abdominal spread.

Published data concerning the outcome of uterine sarcoma after morcellation are not homogeneous. In a large study including 58 patients, the authors (29) found that the median recurrence-free survival of patients with uterine LMS who underwent EMM was significantly shorter than that of patients who underwent total abdominal hysterectomy (10.8 vs 39.6 months). However, the study was not limited to early-stage uterine sarcoma. In contrast, Wais et al. (20) reported no significant difference in survival for patients with FIGO-stages-1 and 2 disease with disruption (n=32) of uterine sarcoma compared to those without tumor disruption (n=143) over a median follow-up period of 2.9 years. The above mentioned reports highlight the need for further investigations focusing on patients with FIGO-stage-1 disease who have undergone surgery, with or without morcellation. Moreover, studies analyzing the outcome of patients with sarcoma after morcellation must be interpreted with caution.

Our homogenous data revealed a slightly better DFS for the non-morcellation group with FIGO-stage-1 uterine sarcoma compared to the morcellation group, but slightly worse OS. However, these differences were not statistically significant. Patients who underwent morcellation were slightly younger than the others (52.8 vs 62.7 years, p=0.074), and younger age is known to be associated with a better outcome (30). Furthermore, the morcellation group had slightly higher rate of LMSs than the non-morcellation group (80 vs 57.1%, p=0.388). However, the proportion of high grade sarcomas (Grading G3), which are associated with poor prognosis, were similar in both groups (20 vs 28%).

Raine-Bennett et al. (31) reported no significant difference in the unadjusted three-year DFS between patients with FIGO-stage-1 uterine sarcoma who did or did not undergo morcellation. In our study, patients who underwent morcellation experienced an intra-abdominal recurrence more often (80%) than did patients in the non-morcellation group (40%). Notably, in two cases, we observed dissemination of sarcoma after morcellation on both sides of the abdominal wall, in the area of trocar placement at the first operation. In contrast, Lin et al.

Table 4. Ultrasound characteristics of patients and survival outcome

Characteristics of the patients	n	Myomas group	Sarcomas group	Total	p
Ultrasound					
Tumor size >8 cm	118	19 (19.8%)	12 (54.5%)	31 (26.3%)	**0.001**
Solitary tumor	119	34 (35.4%)	17 (73.9%)	51 (42.5%)	**0.001**
Irregular lining	120	18 (18.7%)	5 (20.8%)	23 (19.2%)	**0.770**
High vascularization	119	9 (9.4%)	9 (39.1%)	18 (15.1%)	**0.001**
Anechogenic areas with suspicion for necrosis	120	7 (7.3%)	8 (33.3%)	15 (12.5%)	**0.002**
Indications for operation					
Bleeding disorders	120	37 (38.5%)	15 (62.5%)	52 (43.3%)	**0.045**
Uterine growth	120	21 (21.8%)	12 (50.0%)	32 (27.5%)	**0.006**
Type of operation					
Hysterectomy	119	84 (88.4%)	23 (95.8%)	107 (89.9%)	**0.455**
Myomectomy	120	4 (4.2%)	1 (4.2%)	5 (4.2 %)	**0.739**

(24) reported that morcellation of sarcoma did not increase the abdominal pelvic recurrence rate, but may be associated with poorer survival in unexpected FIGO-stage-1 disease. Besides tumor morcellation, any type of tumor injury may aggravate hematogenous spread of tumor cells. The most common site of extra-pelvic recurrence in our patients was the lungs (67%), which is in accordance with the published literature (32). Factors that primarily affect the outcome of disease in patients with uterine sarcoma remain unclear. Notwithstanding the above mentioned negative outcome (33), the rarity of uterine sarcoma and its inherent poor prognosis should not affect the use of MIS for this condition.

We assumed a favorable prognosis for patients who had undergone a second operation with longitudinal laparotomy due to an unexpected morcellated sarcoma. Three patients who did not undergo re-exploration after morcellation of sarcoma experienced recurrent disease within 12 months. Of the remaining seven patients with morcellated sarcoma who underwent a re-exploration, only two experienced a recurrence after 12 months. In a review comprising 47 published studies, Tantitamit et al. (34) reported that early re-exploration (within 30 days) led to lower mortality rates and a better prognosis compared to late re-exploration (>30 days). Based on our data, we conclude that LASH or myomectomy as the first operation was no significant predictor of a poor prognosis when a re-exploration was performed. Our short re-operation interval (2 to 4 weeks) might have contributed to this result. However, the small number of patients does not permit definite conclusions.

Study Limitation

As mentioned, the main limitation of the present study is the small number of patients, which reduced the statistical power of the analysis. Although patients with sarcomas and those with uterine myoma were matched by age and type of operation, factors such as the gynecologists performing the ultrasound examination and the ultrasound device were not matched. On the other hand, detailed preoperative and postopertive information were available for all patients, and both groups of patients were followed up for a relatively long period of time. To our knowledge, published data concerning predictions and the outcome of FIGO-stage-1 uterine sarcoma are limited and inconsistent. Our data contribute significantly to the published literature on the subject.

Conclusion

We were not able to determine patient characteristics that could be clinically useful in the preoperative diagnosis of early-stage uterine sarcoma. Obese women are at no greater risk of developing uterine sarcoma. Ultrasound characteristics, such as solitary and large tumors measuring more than 8 cm in size, with anechoic areas indicative of necrosis and high vascularization, might serve as signs of uterine sarcomas. In addition, a combination of BMI, age, and ultrasound characteristics may enhance the accuracy of preoperative diagnosis of uterine sarcoma. Sarcoma morcellation may increase abdominal pelvic recurrence rates, but may not be associated with OS in patients with FIGO-stage-1 disease. The effects of surgical techniques involving tumor disruption on survival remain controversial. Further studies should be designed to assess the positive effects of re-exploration after morcellation of occult sarcomas. The limited number of cases investigated in the present study, the low incidence of the disease, the level of evidence for risk factor, and the outcome of morcellated uterine sarcoma does not permit any specific recommendations about the treatment of uterine sarcomas. Future studies should be focused on the preoperative diagnosis and outcome of early-stage uterine sarcoma, while the rarity of the disease does not permit prospective investigations.

Ethical Committee Approval: *The study was approved by the Ethical Committee of the Medical Faculty of the University of Luebeck (approval number: 18-115).*

Informed Consent: *It was obtained.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Surgical and Medical Practices: G.G., I.A., A.R., S.S., L.A., S.B., K.E.., K.W., C.K., A.S.L., G.P.; Concept: G.G., I.A., G.P.; Design: G.G., I.A., A.R., K.E.., C.K.; Data Collection or Processing: G.G., I.A., K.E.., K.W., C.K., S.B.; Analysis or Interpretation: G.G., I.A., A.R., S.S., L.A., S.B., K.E.., K.W., C.K., A.S.L., G.P.; Literature Search: G.G., I.A., S.B., K.E.., G.P.; Writing: G.G., I.A., A.R., S.S., L.A., S.B., K.E.., K.W., C.K., A.S.L., G.P.*

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

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

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Partial mole with coexistent live fetus: A systematic review of case reports

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Abstract

Objective: Molar pregnancy coexistent with a live fetus can be a diagnostic and therapeutic challenge. With increasing incidence of multiple pregnancies, there has also been an increase in twin pregnancy with one mole in the recent years. The authors discuss the epidemiology, clinical presentation, and prenatal diagnosis and attempt to design a possible management strategy, to help guide the treating physician, in the management of partial mole with live pregnancy, thereby improving maternal and fetal prognosis.

Material and Methods: Numerous case reports have been published in various journals regarding management of individual cases of partial molar pregnancy coexistent with live fetus (PMCF). Therefore, we conducted a systematic review of all the case reports and short case series in English concerning partial mole with live pregnancy from 1999 to 2019, that is in the last 20 years.

Results: In total, 44 case reports of PMCF were analyzed. The mean gestational age at diagnosis was 20+6 (range: 10-40) weeks. Less than half (19/44; 43.2%) were asymptomatic at the time of detection and PMCF was detected on routine scan done for fetal well-being or 11-13-week scan. The majority (56.8%) resulted in the birth of a healthy live fetus. Gestational trophoblastic neoplasia developed in 3/44 (6.8%).

Conclusion: PMCF involves a high risk of bleeding, preterm labour, intrauterine growth restriction and stillbirth. Successful management of such cases needs prenatal diagnosis, antepartum surveillance and post-natal follow-up. An obstetrician, maternal fetal medicine specialist, gynecology oncologist and neonatal intensivist should be involved in the care of such pregnancies. (J Turk Ger Gynecol Assoc 2022; 23: 83-94)

Keywords: Partial hydatidiform mole and coexistent live fetus, GTN, partial molar pregnancy, sad fetus syndrome

Received: 02 November, 2021 **Accepted:** 20 March, 2022

Introduction

A molar pregnancy coexistent with a live fetus, also known as sad fetus syndrome is a rare phenomenon with an incidence reported to be approximately 0.005-0.01% of all pregnancies (1). Molar pregnancy results from genetically aberrant conceptus. Usually, the complete mole has 46 chromosomes but all are of paternal origin, as an empty egg is fertilized by a sperm with duplicate genetic material. A partial mole usually results from dispermic fertilization of a haploid normal ovum resulting in a triploid zygote or monospermic fertilization with duplication of the paternal haploid chromosome, whereas the complete mole is result of fertilization of an empty ovum by a sperm (2). Though much rarer, there can be cases of mitotic abnormalities in the early post fertilization period, a form of placental mosaicism (3,4). USG in early pregnancy is the diagnostic tool to detect the majority of molar pregnancies. Though molar pregnancy can have varied presentation, most molar pregnancies present either as missed miscarriage or anembryonic pregnancy. Suction evacuation of products of conception followed by histopathology is confirmatory for diagnosis of a molar pregnancy (5). Women carrying a female fetus are more likely to have partial mole than mothers carrying a male fetus, with a ratio of 3.5:1 (1).

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Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2022.2021-9-11

There is evidence in cases of twin pregnancy when one fetus dies in utero, the effect on the other fetus may be the immediate demise of the other twin, an effect on cognitive development of the surviving twin and/or effects on the maternal coagulation system. With the increasing incidence of multiple pregnancies, mainly as a result of assisted reproductive technologies, there has been an increase in the twin pregnancy rate with one fetus presenting as partial mole in the recent years. These pregnancies are considered high risk pregnancies and need thorough counselling (6). Though termination of pregnancy remains an option taking into account the high incidence of complications in these pregnancies, many women, especially those who conceive after years of infertility treatment, may choose not to go for termination. There should be informed decision making after providing adequate information about the chances of a live birth (about 50%) and risk of maternal and fetal complications (7). One of the major concerns in these women is the risk of gestational trophoblastic neoplasia (GTN), and whether this risk will increase further with continuation of pregnancy needs to be discussed with individual patients. GTN in general can have a varied clinical presentation and can present at variable interval of time after index pregnancy (8).

From the clinical perspective, pregnancy with partial mole can be of the following two types. The most common type is a dichorionic twin pregnancy with one sac containing a normal euploid fetus and placenta and the other sac containing the molar pregnancy, which can be either complete or partial mole. The other possibility is a singleton pregnancy with focal areas of degeneration affecting small to large placental areas (9).

It is very important but difficult to differentiate a singleton pregnancy with focal molar changes in the placenta from a twin pregnancy with one normal fetus and the other complete mole. A method which has been suggested to differentiate the two conditions is to follow the placental insertion site of the umbilical cord and, if it attaches to the molar placenta, it suggests singleton pregnancy with focal mole whereas if it attaches to a normal placenta it is more suggestive of twin gestation (10). Other important differential diagnosis of partial mole in case of twin pregnancy includes placental mesenchymal dysplasia (confirmed on histopathology) (11,12). Differential diagnosis also includes placental tumor, such as chorioangioma. However, this is usually a well circumscribed lesion with a different echogenicity from the rest of placenta, protrudes into the amniotic cavity, shows increased vascularity along with a feeding vessel with flow synchronous with the umbilical artery on Doppler (13).

Cases of partial mole with a coexistent live fetus (PMCF) present a diagnostic and management challenge to the treating obstetrician. Most of the literature available is in the form of case reports with varied presentation. Therefore, we performed a systematic review of cases of PMCF published in the last 20 years to examine the epidemiology, clinical presentation, prenatal diagnosis and to attempt to define a possible management strategy, to help guide the treating physician, thereby improving maternal and fetal outcome.

Material and Methods

This being a systematic review of case reports ethics committee approval was not sought as systematic reviews are exempted from ethics review.

An electronic search of Scopus, PubMed, Embase and other databases was conducted for case reports and case series of PMCF, published in English from 2000 to 2019. The electronic search strategy was done using keywords, such as “partial mole with live fetus” and “mole with live fetus”, “twin pregnancy with partial mole” and “hydatiform mole”, and “coexistent fetus” and “sad fetus syndrome” and “case reports”. We analyzed the title and abstracts of all case reports identified by the initial search. The reference lists of relevant reports were also explored. The data was double checked by two reviewers to avoid duplication.

The systematic review was planned and reported according to the preferred reporting items for systematic review and meta-analyses guidelines.

Published case reports and case series of partial mole coexistent with a live intra-uterine pregnancy at all gestational age were included in this systematic review. Case reports with complete hydatidiform mole coexistent with live fetus and case reports of partial molar pregnancy without live fetus were excluded. Review articles, original articles, clinical trials, conference abstracts, editorials, poorly described cases, articles in language other than English language or commentary were also excluded.

We extracted information, such as geographical distribution or country of occurrence of the case, year of publication, age of the patient at the time of presentation, gestational age at diagnosis, the time of delivery and the final outcome of the case in the form of live birth or abortion or induced termination and summarized it in a master chart. The various obstetric and medical complications that developed during the course of pregnancy were documented, such as miscarriage and gestational age at the time of miscarriage, pre-eclampsia and gestational age at which it developed, gestational diabetes, intra-uterine growth restriction, stillbirth, and preterm labor before 37 completed weeks of gestation. A note was also made of whether or not the patient developed GTN after termination of pregnancy and, if they did, the type of GTN and how long after termination of pregnancy GTN developed. Descriptive statistics was used to

calculate simple frequency, percentage, and proportion out of the total case reports.

Results

A brief overview of the article screening process is shown in Figure 1. A total of 260 articles were identified on initial electronic database search, of which 41 articles, with a total of 44 cases of PMCF were included in the final analysis.

Demographic characteristics

The geographic distribution of cases is shown in Figure 2 with the age distribution shown in Figure 3. The majority of the cases reported were aged between 26 and 30 years. This also represents the age when most pregnancies happen. The mean gestational age at diagnosis was 20+6 weeks ranging from 10-40 weeks.

Clinical manifestations

Less than half of the cases (19/44, 43.2%) were asymptomatic at the time of diagnosis and were detected incidentally during routine ultrasonography (USG) scan done for fetal well-being or at 11-13th week combined screening test. The diagnosis was made as early as 10 weeks of gestation in two patients because of the appearance of multiple cystic spaces in the placenta. Interestingly, both these patients were women with Turner syndrome mosaicism and pregnancy was a result of intracytoplasmic sperm transfer in both. False positive first trimester screen for Down syndrome and cystic hygroma at 11-14th week scan and hydrops raised suspicion in two cases. The most common clinical manifestation (13/44; 29.5%) that caused suspicion and eventual diagnosis was vaginal bleeding. Nine (69%) had bleeding in the first trimester and presented with threatened miscarriage. Two (15.4%) had vaginal bleeding in the second trimester and two further patients presented with ante-partum hemorrhage in the third trimester. Preeclampsia and eclampsia (5/44; 11.4%), hyperemesis (3/44; 6.8%) and hyperthyroidism (2/44; 4.5%) were other common manifestations. One patient was diagnosed due to progressive anemia as a result of feto-maternal hemorrhage. Preterm labor, intrauterine fetal demise and vanishing twin were the presenting clinical

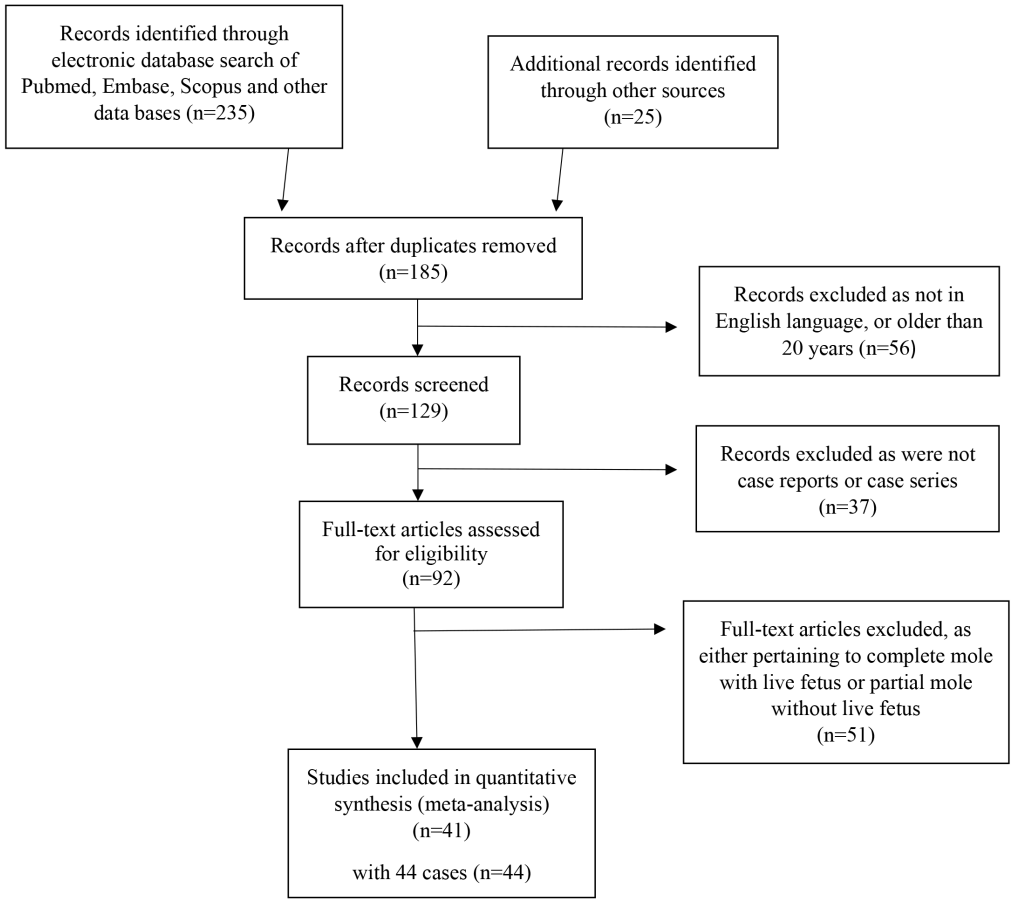

Figure 1. PRISMA flow chart

PRISMA: Preferred reporting items for systematic review and meta-analyses

manifestations in one case each, which raised suspicion leading to diagnosis of partial mole (Figure 4).

Diagnosis

Of 44 cases, the diagnosis was made on USG examination in 36 (81.8%). In approximately 43% of cases (19/44), it was an incidental finding on routine USG examination, while others were detected on a detailed examination done due to vaginal bleeding or cystic hygroma, hydrops, placentomegaly or unusual elevation in the levels of beta-human chorionic gonadotropin (β-hCG). Four cases were detected only on the pathological examination of the placenta after delivery. The presence of grape-like vesicles or cystic areas in the placenta on gross examination, fetal growth restriction or unexplained fetal anemia due to feto-maternal hemorrhage raised suspicion, thereby prompting histopathology. On gross examination, the partial mole was focal in 11 cases and did not involve the entire placenta.

Out of 44 cases, the karyotype of the fetus was normal in 29 (65.9%). Among those with abnormal fetal karyotype, one fetus had trisomy 21, one had monosomy X, two had triplody and in three patients, although the placenta was triploid, fetal karyotype was diploid. One case of Dandy-Walker malformation was also reported with diploid fetus. Karyotype was not done or not mentioned in 11 patients.

The structural congenital anomalies associated were cystic hygroma, omphalocele, hydrocephalus, meningomyelocele, spina bifida, congenital talipes equinovarus and hypospadias.

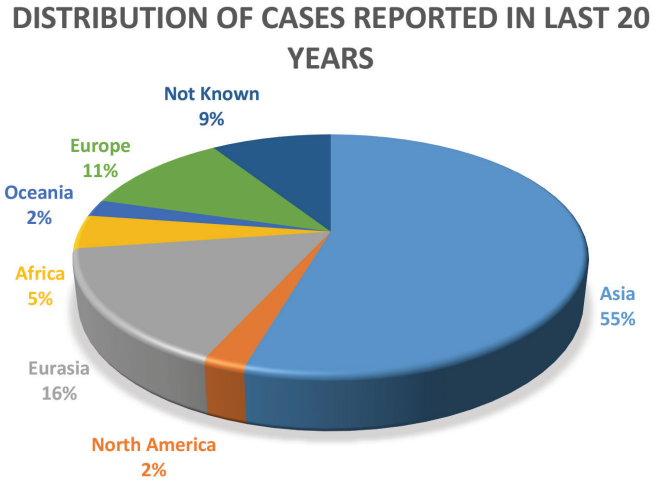

Figure 2. Geographical distribution of cases of partial mole with live fetus in last 20 years

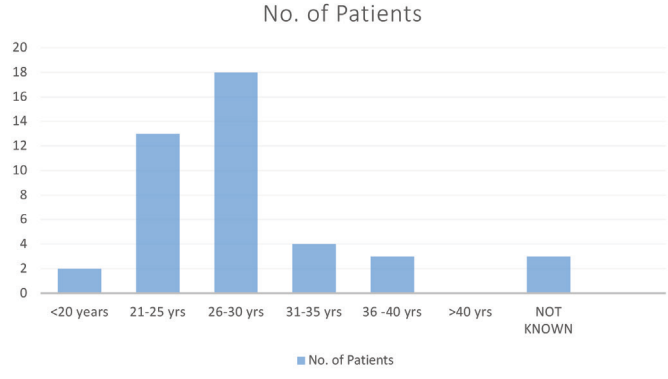

Figure 3. Age distribution of cases of partial mole with live fetus reported in literature in last 20 years

Fetal and maternal outcome

Figure 4 illustrates the major maternal and fetal complications seen in cases of partial mole with one live fetus. Twenty-five (56.8%) resulted in live birth, athough there was one case of early neonatal death. Two babies were born with severe anemia and required multiple transfusions after birth, but survived. One baby died after 65 days of life due to respiratory failure because of hyaline membrane disease and severe hypothermia. Intra uterine death of fetus was reported in six cases, and pregnancy was terminated in 12 cases mainly due to excessive bleeding complications.

Thirteen patients delivered vaginally, nine out of these after 34 weeks of gestation. Four were preterm deliveries: two patients went into spontaneous preterm labour at 28 weeks, one at 30 weeks of gestation and one woman delivered at 24 weeks due to vaginal bleeding followed by preterm labor. Twelve patients were delivered by Caesarean section (CS), the most common indication for CS being excessive vaginal bleeding or antepartum hemorrhage. Ten out of these 12 CSs were done preterm, from 26 to 32 weeks of gestation. Other common indications for CS were severe growth restriction, compromised Doppler and prematurity. In 11/12 (91.7%), the birth weight was less than 10th centile with four out of these having birth weight less than 3rd centile.

One patient underwent emergency hysterectomy and internal iliac artery ligation as a consequence of excessive haemorrhage associated with placenta accreta in a woman with PMCF. Theca lutein cysts were found in 4/44 (9.1%). Two out of 44 (4.5%) developed hyperthyroidism that was managed medically with propylthiouracil in both.

Follow-up

Complete β-hCG follow-up was not mentioned in all cases. The duration from pregnancy termination until undetectable β-hCG values was available for 21/44 cases. GTN was reported in 6.81% (3/44). All three patients developed choriocarcinoma which responded completely to chemotherapy. Persistently raised β-hCG on follow-up, associated with vaginal spotting, was the main presentation, which led to the diagnosis of GTN. The time duration between termination of pregnancy and development of GTN was one month in two cases and two

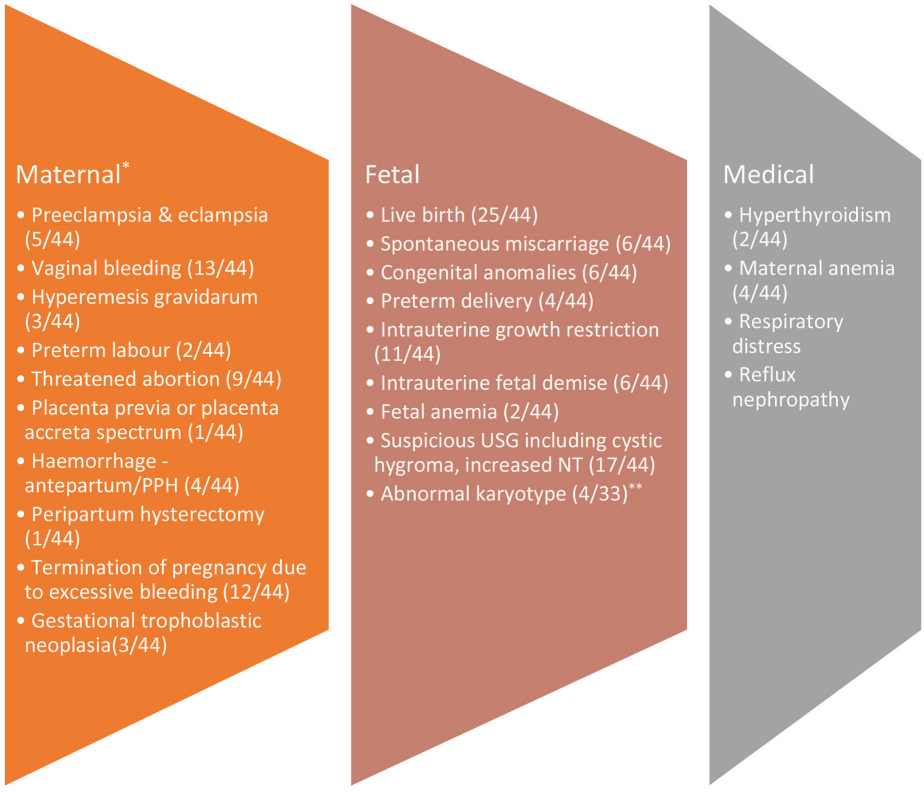

Figure 4. Maternal and fetal complications associated with live pregnancy with partial mole
***Majority less than half were diagnosed as incidental finding on USG (19/44), **in 11 cases fetal karyotype was not done or documented**

USG: Ultrasonography

months in the third case. There was no sign of residual disease or recurrence in any of these three patients after completion of chemotherapy (Table 1).

Sixteen case reports mentioned about follow-up after normalization of β-hCG values. Duration of follow-up was five years in one, two years in three, one year in seven and six months or less in the remaining five cases reports. Four case reports mention follow-up until time of publication, but this makes it difficult to estimate the actual follow-up duration as publication delay was unknown (Table 1).

Discussion

We present here a comprehensive systematic review of published case reports of PMCF in the last 20 years. There were only 44 such cases worldwide published in English, over a period of 20 years, suggesting the rarity of this entity. Therefore, this systematic review will help to aid in understanding the epidemiology, clinical presentation, and prenatal diagnosis and may help to identify a possible management strategy.

Most cases (55%) were reported from Asia. This correlates with the geographical distribution of molar pregnancy. The incidence of molar pregnancy is higher in Asia, compared to Europe and North America (9). This epidemiological distribution might be affected by the reporting system of each country.

The most common presenting complaint was vaginal bleeding, although it affected less than a third of cases. This correlates with the large placental size, cystic changes in the placenta and the non-viability of the molar tissue. The bleeding in these cases may present at any time during pregnancy. In our case series, the earliest presentation was in the first trimester as missed miscarriage associated with vaginal bleeding and patients presented in the late third trimester with antepartum haemorrhage. Bleeding in the first or second trimester of pregnancy is one of the most common complications in such cases. Bleeding at any time may prove life threatening for the mother, thereby necessitating urgent delivery (14). The large size of placenta also increases the chances of placenta previa (15) and other placental abnormalities, such as circumvallate placenta. Ante-partum and post-partum hemorrhage necessitating massive transfusions or even emergency hysterectomy has been reported.

Clinical presentation may be diverse. Less than half of the cases (43%) in the present systematic review were diagnosed

Table 1. Summary of clinical parameters of included case reports

Author, year	Maternal age (years)	Gestational age at delivery/ termination (weeks)	Cytogenetical analysis	Pregnancy outcome	Beta HCG at presentation (mIU/mL)	Follow-up beta HCG (time following pregnancy termination)	Total duration of follow-up (after normalization of beta HCG)
Rahamni and Parviz (37), 2016	26	26	Normal	IUD, preterm delivery	64750	Undetectable at 1 month	6 months
Gupta et al. (38), 2015	30	13+3	-	Spontaneous abortion	180000	Undetectable at 8 weeks	NA
Hassan et al. (39), 2018	25	18+6	-	Spontaneous abortion	561771	24 hours- 210310 Undetectable at 6 weeks	NA
Rathod et al. (6), 2014	-	34	Normal	Preterm delivery	23500	UPT negative at 6 weeks	12 months
Chu et al. (40), 2004	29	24	Mole - XXY, Fetus XY	Preterm delivery	-	Normal at 1 month (7 mIU/L)	NA
Göksever Çelik et al. (41), 2017	27	12	-	Spontaneous abortion	606104	10 days - 7538, 18 days - 1373, and at 25 days - 364	On F/U at time of reporting-exact duration not mentioned
Rathod et al. (42), 2015	24	28	-	Preterm delivery	121993	Undetectable at 4 weeks	On F/U at time of reporting-exact duration not mentioned
Ara et al. (43), 2016	26	40	Normal	Term delivery	-	-	12 months
Tesemma (16), 2019	18	34	-	Preterm delivery	-	48 hours - 162, normal at 3 weeks, undetectable at 3 months	NA
Koregol et al. (44), 2009	22	31	-	Preterm delivery followed by early neonatal death	-	-	NA
Shobha et al. (45), 2010	21	37	-	IUD, term delivery	1600247	-	NA
Rao et al. (18), 2015	24	32	Normal	Preterm delivery	603360	-	NA
Rao et al. (18), 2015	27	27	Normal	IUD, preterm delivery	192640	Declined initially F/B rise after 15 days, Was given 2 doses of methotrexate	12 months
Rai et al. (46), 2014	25	36	-	Preterm delivery	374747 declined in 2nd trimester with decrease in size of theca lutein cysts.	1 week - 111, Normal - 3 weeks post-partum	On F/U at time of reporting-exact duration not mentioned

Table 1. Continued

Author, year	Maternal age (years)	Gestational age at delivery/ termination (weeks)	Cytogenetical analysis	Pregnancy outcome	Beta HCG at presentation (mIU/mL)	Follow-up beta HCG (time following pregnancy termination)	Total duration of follow-up (after normalization of beta HCG)
Sun et al. (47), 2012	32	35	Mole 69XXY, Villi 46XY	Preterm delivery	-	Undetectable at 6 months	NA
Guven et al. (48), 2007	21	28	Normal	IUD, preterm delivery	499000	-	NA
Lembet et al. (15), 2000	28	21	Normal	Induced abortion	79.642	7 weeks	2 years
Atuk and Basuni (49), 2018	21	28	Normal	Preterm delivery followed by early neonatal death on day 12	NA	4 weeks	NA
Kawasaki et al. (22), 2016	27	25	Placenta 69XXX, Fetus 46 XX	Preterm delivery	468185	-	NA
Copeland and Stanek (50), 2010	29	28	Placenta triploid, Fetus diploid	Preterm delivery	NA	-	NA
Agarwal et al. (51), 2005	-	28	Normal	Preterm delivery		-	NA
Sak et al. (52), 2012	28	37	Normal	Term delivery	94753	2 weeks	NA
Hsieh et al. (53), 1999	30	32	Normal	Preterm delivery	167596	4 weeks	NA
Shiina et al. (54), 2002	23	20	Normal	Induced abortion	603.84	At 3 weeks - 6584 At 5 weeks - 8830 Developed GTN Received chemotherapy Undetectable at 22 weeks	2 years
De Franciscis et al. (55), 2019	37	31	Normal	Preterm delivery	14898	-	12 months
Santos et al. (17), 2017	28	20	69XXX	Induced abortion	1891264	At one-month 520 mIU/mL	6 months
Singh et al. (56), 2017	24	21	Trisomy 21	Hysterotomy	424249	8 weeks	1 year
Fdil et al. (57), 2018	26	14	Placenta 69XXY, Fetus diploid	Spontaneous abortion	72000	5 weeks	6 months
Park et al. (20), 2018	37	12	45X Turner	Induced abortion	50,000	12 weeks	2 year
Sargin et al. (19), 2015	27	11	-	Induced abortion	550000	12 weeks	1 year
Abukaftah et al. (58), 2018	40	28	Normal	Preterm delivery	106000	-	NA

Table 1. Continued

Author, year	Maternal age (years)	Gestational age at delivery/ termination (weeks)	Cytogenetical analysis	Pregnancy outcome	Beta HCG at presentation (mIU/mL) CGHCG	Follow-up beta HCG (time following pregnancy termination)	Total duration of follow-up (after normalization of beta HCG)
Parveen et al. (59), 2004	23	39	Normal	Term delivery	Not performed	UPT negative at 6 weeks	4 months
Dhingra et al. (60), 2009	28	38	Normal	Term delivery	NA	NA	NA
Dhingra et al. (60), 2009	22	34	Normal	Preterm delivery	NA	NA	NA
Rato et al. (61), 2014	30	37	Normal	Twin 1- IUD at 18 weeks Twin 2-Term delivery	-	-	NA
Shiozaki et al. (23), 2012	30	20	Normal	Induced abortion	-	-	NA
Tamrakar and Chawla (62), 2011	26	32	Normal	Preterm delivery	Not performed	UPT negative at 3 weeks	5 years
Papoutsis et al. (21), 2011	31	30	Normal	IUD, preterm delivery	34554	4 weeks	Normal ever since as per the authors
Allgayer et al. (63), 2010	-	40	Normal	Term delivery	449503	-	NA
Allgayer et al. (63), 2010	-	27	Normal	Preterm delivery	-	-	NA
Unsal et al. (14), 2010	32	13	-	Spontaneous abortion Acute hemorrhage during evacuation due to placenta accreta, hysterectomy was performed	-	-	NA
Sánchez-Ferrer et al. (64), 2009	25	21	Normal	Spontaneous abortion	365,745	After an initial decline to 3000, beta HCG increased to 9000. Developed GTN Required 7 cycle of chemotherapy	On F/U at time of reporting-exact duration not mentioned
van der Houwen et al. (65), 2009	33	38	Normal	Term delivery	423000	At 4 days -440	NA
Ingec et al. (66), 2006	17	11	-	Induced abortion	276079	At 2 weeks - 5457, Then lost to F/U At 2 months - 6690 Developed GTN Received 2 courses of chemotherapy	1 year

USG: Ultrasound, HPE: Histopathology, IUD: Intrauterine death, F/U: Follow-up, NA: Not available, UPT: Urine pregnancy test, GTN: Gestational trophoblastic neoplasia

incidentally as a result of routine USG done in early weeks of gestation. Hyperemesis, early onset preeclampsia and eclampsia (16,17), hyperthyroidism (11), unexplained intrauterine fetal demise (18) or fetal growth restriction, preterm labor or premature rupture of membranes (6), and pain in the lower abdomen, were the other presenting complaints. Rarely, cases attracted clinical attention due to positive first trimester screen or detection of cystic hygroma or fetal hydrops on USG examination (19,20). Partial mole may be detected incidentally on gross or pathologic examination of the placenta. There should be a high index of suspicion in cases with fetal or neonatal anemia or unexplained intra uterine death of fetus (21). Rarely, PMCF was reported to be complicated by progressive anemia (22) or respiratory distress (23).

Cystic changes in the placenta or placentomegaly are one of the earliest USG findings that attract attention. A large sized placenta also predisposes to placenta previa and even cases of morbidly adherent placenta necessitating emergency peripartum hysterectomy have been reported (24). There was one case of one patient undergoing peripartum hysterectomy and internal iliac artery ligation for antepartum haemorrhage associated with placenta accreta.

Although USG is the initial modality of choice for the diagnosis of molar pregnancy, the sensitivity is only 40-60% (25). Detection rate on USG is higher for complete moles than for partial moles, as most partial moles may be mistaken sonographically as missed or incomplete abortions in early pregnancy, as the appearance is quite similar (26,27). However, the following features on USG have been said to be suggestive of partial mole:

a. thickened placenta with hypoechoic areas (11);

b. absent or low venous flow inside the placental lesion, especially during the first two trimesters, helps to differentiate it from chorioangioma or complete mole (28);

c. increased echogenicity at the maternal fetal interface;

d. altered gestational sac diameter ratios, cystic changes in the placenta or snow storm appearance (28).

The definitive diagnosis of partial mole can be established only by a pathological examination of the placenta (29). Immunohistochemical analysis for p57 protein, which is expressed only from the maternally derived antigens, may be helpful to differentiate partial from complete mole, especially in cases that are difficult to diagnose by USG alone. This is becoming increasingly important as with earlier diagnosis and therapeutic termination, the differentiation of molar from non-molar pregnancy has become difficult. As complete mole lacks a maternal genome, $p57^{KIP2}$ immunostaining will be absent, whereas hydropic abortuses and partial mole show positive staining. Positive p57 staining has high sensitivity and specificity to exclude the diagnosis of complete mole (30,31). So, p57 staining complements the ploidy studies to refine the diagnosis of early molar pregnancies.

The diagnosis of PMCF can also be suspected on the basis of abnormal prenatal screening testing results. Single nucleotide polymorphism-based, non-invasive prenatal testing has the potential to detect uniparental diosomy, which is the hallmark of complete molar pregnancy (32), and can also detect cases of both diandric or digynictriploidy, characteristic of partial mole (33,34).

Preeclampsia is thought to be mediated by circulating factors of placental origin, mainly sFlt-1 and S-endoglin. The sFlt-1: placental growth factor ratio are also usually extremely high and are one of the factors implicated in early onset preeclampsia before 20 weeks of gestation (17).

Live birth rate was 56.8%, whereas intrauterine death was reported in 20% of cases. Pregnancy was terminated in 27% due to excessive vaginal bleeding. Mode of delivery depends upon the maternal and fetal condition. In published cases, CS was performed mainly for antepartum hemorrhage. One patient required emergency hysterectomy and internal iliac artery ligation due to associated bleeding with placenta accreta.

Cases of PMCF are at high risk for developing GTN, which occured in 7% of the cases reviewed. All three patients developed choriocarcinoma which completely responded to chemotherapy. Histopathological examination of placenta and strict follow-up with β-hCG monitoring is necessary for timely identification of the development of GTN and the success of treatment.

The decision to continue pregnancy is very much dependent on the karyotype of the fetus. The best method to determine the fetal karyotype still remains controversial. Although chorionic villus sampling has an advantage of diagnosis at an earlier gestational age, it may not be diagnostic of the fetal karyotype due to confined placental karyotype aberration. Amniocentesis remains the diagnostic test of choice. Therefore, USG guided placental biopsy, fetal karyotype by either amniocentesis or fetal blood sampling, combined with serum monitoring for β-hCG should be used to guide decision making (15).

Management strategy

Sad fetus syndrome, or live pregnancy with coexistent mole is a rare entity, yet poses a great diagnostic and management challenge to the obstetrician. Here we propose a management plan on the basis of the available evidence obtained from this literature review.

A high index of suspicion should be kept in all cases at extremes of age, in mothers of Asian origin, women with multiple pregnancies, those who conceived by assisted reproductive methods or those presenting with bleeding in early pregnancy. A USG examination of both the fetus and placenta should be

performed. All cases presenting with cystic changes in the placenta should have a detailed examination to see whether the changes are focal or complete and whether a live fetus coexists with a molar pregnancy. Cord insertion should be looked for, if it inserts on the cystic placenta, a focal mole is more likely and if the cord inserts on a normal placenta, a twin pregnancy with coexistent mole is an option. Women should be counselled about all the complications that can develop during the course of continuing this pregnancy, including the risk of GTN, and need for chemotherapy if it occurs. The risk of triploidy and congenital anomalies in the fetus, preterm labor, fetal growth restriction, intra uterine fetal demise, ante-partum or post-partum hemorrhage any time necessitating urgent delivery or peripartum hysterectomy should also be discussed with the patient.

Factors that should be kept in mind when counselling patients regarding fetal prognosis include the karyotype of fetus (6), parity of the woman, coexistent obstetric and medical complications and the rate of degeneration of molar tissue.

If the patient decides to continue with the pregnancy, these patients might need multidisciplinary care throughout the pregnancy. An obstetrician, maternal fetal medicine specialist, gynecologic oncologist and neonatologist should be involved in the care of such a pregnancy.

An amniocentesis at around 16 weeks to determine fetal karyotype, detailed USG to rule out any congenital abnormalities in the fetus, including fetal echocardiography, should be offered. Serial scans for fetal growth may be needed every 2-3 weeks, as these fetuses are very high risk for fetal growth restriction and oligohydramnios. These fetuses should be under strict surveillance for impaired circulation due to abnormal development of villi; they are at very high risk for sudden death or still-birth. These women are at risk of torrential life-threatening hemorrhage at the time of delivery. Therefore, all necessary preparations should be made beforehand. If an elective CS is planned, especially in the setting of previous two or three Caesareans, pre-operative balloon catheters in the uterine or internal iliac arteries might be needed in order to minimize blood loss. Uterine artery embolization has a role in cases of excessive hemorrhage associated with molar pregnancy (35). An adequate amount of blood should be cross matched and be available at the time of delivery, should the need arise.

Even after delivery, the patient needs weekly β-hCG monitoring for early diagnosis and management of post molar GTN and single additional confirmatory normal β-hCG measurement one month after the first normalization of β-hCG after a partial mole and for at least six months after a complete mole (36).

Study Limitations

The present systematic review provides the most recent and comprehensive overview of epidemiology, clinical manifestations, prenatal diagnosis and management in cases of PMCF. All globally published cases in English have been identified by extensive electronic database searches. However, the data was heterogeneous, and the analysis was descriptive, which are limitations of this systematic review. Case reports and case series published in other languages were not included, which might be another limiting factor.

Conclusion

PMCF should be considered as a high-risk pregnancy. A high index of suspicion is required for timely diagnosis and successful management. Prenatal diagnosis and counselling, strict antepartum surveillance and adequate post-natal follow-up play a vital role in optimal maternal and fetal outcome. An obstetrician, maternal fetal medicine specialist, gynecologic oncologist and neonatologist should be involved in the care of such a pregnancy.

Ethics Committee Approval: *This being a systematic review of case reports ethics committee approval was not sought as systematic reviews are exempted from ethics review.*

Informed Consent: *It wasn't obtained.*

Peer-review: *Externally peer-reviewed.*

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

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

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

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What are the advantages of clock position method to determine fetal heart axis for inexperienced resident physicians? A comparative study

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Abstract

Objective: Residency training programs are challenging for young physicians with heavy workloads. Although ultrasonography (USG) is an imaging method that is frequently used in obstetrics practice, some basic USG skills can be acquired late in this intensive learning process. Likewise determining the fetal heart axis is an elementary evaluation but can turn into a challenging and time-consuming process, especially for inexperienced clinicians.

Material and Methods: Pregnant women between 20 and 37 weeks of gestation were recruited. Two observers assessed the axis of fetal heart by standard, Bronshtein and clock position methods. Fetal heart axis evaluation times were compared. Inter-observer and intra-observer agreements of the three methods were measured. One factor learning rates were calculated.

Results: A total of 31 pregnant patients between the ages of 18 and 40 years were included in the study. Fetal heart axis evaluation time by the clock position method was shorter than the Bronshtein and standard method in both observers. Furthermore diagnostic accuracy for both observers was 100% with the clock position method, while this fell to 100% in observer-1 and 96.8% in observer-2 using the Bronshtein method. The clock position method was learned faster than either of the other methods.

Conclusion: Clock position method is an easy and feasible method for inexperienced resident physicians in terms of learning and application to determine the fetal heart axis. The advantages of this method increase when patient numbers are higher.
(J Turk Ger Gynecol Assoc 2022; 23: 95-8)

Keywords: Fetal heart axis, ultrasonography, residency training, fetal situs, learning curve

Received: 13 December, 2021 **Accepted:** 09 March, 2022

Introduction

Residency training programs are challenging for young physicians, due to heavy workloads and the intensive learning process. In obstetrics and gynecology residency programs, inexperience with the use of ultrasonography (USG) equipment and insufficient general obstetrics and gynecology knowledge can cause many mistakes and become a source of stress for young residents (1). For this reason, it is necessary to implement practices that will both reduce the pressure on residents and prevent possible medical errors.

USG is an imaging method that is frequently used in obstetrics practice. Therefore, every obstetrician and gynecologist should improve their USG knowledge and skills. The determination of fetal heart axis using USG is an important step in the detection of fetal cardiovascular diseases and organ malrotation (2). The

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Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2022.2021-12-3

situs of the fetus, extension of the fetal spine, and location of organs, such as the stomach, are necessary for the detection of the fetal heart axis. However, this algorithmic approach can turn into a challenging and time-consuming process, especially for inexperienced clinicians. In addition, it may be more difficult to determine the axis of the fetal heart in cases where other organs are located in different locations (3). In situs inversus cases, for example, diagnosis can be easily missed.

Although basic evaluation of the fetal heart is essential, in most cases it cannot be done properly until the end of the residency program. The fact that fetal heart assessment is relatively difficult is one of the main reasons for this situation, but it is also possible because some basic USG skills can be acquired late in training (4). Likewise, determining the fetal heart axis is also an elementary but time-consuming assessment to be made at the beginning.

There are two known methods to distinguish the fetal heart axis. The standard method is the imagination of fetal heart location after the determination of fetal situs. Another method, described by Bronshtein et al. (5), is based on the clinician's use of his forearm and hand to simulate the fetal situs and then the fetal heart axis. In 2018, Dursun and Aktoz (6) described a new technique to determine fetal heart axis, the clock position method. Since then, the clock position method has been frequently used in our clinic and is preferred, particularly by residents who are new to the program.

The aim of this study was to compare the clock position method with the standard method and the Bronshtein method in terms of ease of learning and application.

Material and Methods

This prospective study was performed in a single clinic, between September and October 2021, and approved by the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital Local Ethical Committee (approval number: 78, date: 28.04.2021).

Pregnant women, between 20 and 37 weeks of gestation, were included in the study. The demographic information of the patients (age, gestation week, gravidity, parity) who met the inclusion criteria were recorded. Then, the patients were evaluated by transabdominal USG by two residents who had just started the training program and were not trained in fetal heart evaluation. All patients were evaluated by two observers at different times in different rooms. Informed consent was obtained from all participants.

The axis of fetal heart was determined by using three methods, the standard method, the Bronshtein method and the clock position method. Each method was explained to the residents by a senior obstetrician who also recorded evaluation data. Methods were named as the first, second and third method. The order of application of the methods was randomized using a random sequence generator. In order to avoid bias, the residents were not told that one of the methods was first described by the authors (6). Moreover, the authors were not present in the examination room during evaluation.

The first method was distinguishing the fetal heart axis after fetal situs determination, the second method was the technique defined by Bronshtein et al. (5), and the third method was the clock position method (6).

In the Bronshtein method, the clinician is oriented to the fetus using his hand and forearm. The right hand is used for transabdominal evaluation and the left hand is used for transvaginal evaluation. The dorsal side of the forearm represents the fetal back, while the thumb points towards the fetal heart.

In the clock position method, the ultrasonographic transverse plane of the fetus is considered like a clock dial with the fetal vertebrae at 12 o'clock. In the vertex presentation, fetal heart axis is at 5 o'clock. In the breech presentation, fetal heart axis is at 7 o'clock. If the fetus is in transverse situs, the closest part of the fetus to the maternal right side is accepted as the presenting part. Then, the ultrasound probe is rotated 90 degrees and scanned from the maternal right side to the left.

Statistical analysis

Age, gestation week, gravidity and parity are given as median and interquartile range (25^{th}-75^{th} percentile) while presentations were given as number (%) as demographic characteristics of cases. Fetal heart axis evaluation times (seconds) were compared by Friedman test and by Wilcoxon test post-hoc. Inter-observer and intra-observer agreements of the three methods were measured by Cohen's kappa test. One factor learning rates were calculated by Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA) as the reduction of evaluation time when accumulated evaluation is doubled (7). According to this formulation, a low rate was accepted as a better outcome. All statistical analysis were performed using SPSS, version 17.0 (SPSS Inc., Chicago, IL., USA) and a p value <0.05 was considered significant.

Results

Demographic characteristics of the 31 pregnancies are given in Table 1. The most common fetal presentation was vertex (58.1%) followed by breech (25.8%) and transverse (16.1%). Overall fetal heart axis evaluation time via the clock position method was shorter than Bronshtein method and standard method for both observers ($p<0.001$ and $p=0.001$, $p<0.001$ and $p=0.004$, respectively) (Table 2).

The clock position method diagnostic accuracy was 100% in both observers while for the Bronshtein method diagnostic

accuracy was 100% in one and 96.8% in the other. Observer-2 was not able to determine one of the left fetal heart axis via Bronshtein method. There was no discordance between the three methods while Kappa coefficients were 1 for inter-observer and intra-observer agreements.

The clock position method was also learned faster than the standard and Bronshtein methods. As the number of patients increased, the most successful method in terms of time-based effort was the clock position method with the lowest learning curve rate (95.0%, 97.6%, 88.0% for standard, Bronshtein and clock position methods, respectively) (Figure 1).

Discussion

The clock position method was found to be faster to perform than either the standard method or the Bronshtein et al. (5) method to determine the axis of the fetal heart. This result shows that the clock position method may be advantageous for inexperienced clinicians because it saves time and is easy to apply. In addition, the clock position method was the easiest to learn compared to the other methods. Finally, the fetal heart axis was correctly determined in all patients, as with the method of determining fetal heart axis according to fetal situs (the standard method). In the Bronshtein method, however, one observer could not determine the fetal heart axis in one patient.

Although the Bronshtein method has some advantages for determination of fetal heart axis, it does not provide a faster evaluation than the standard method, based on the determination of fetal situs, as seen in this study. Also, if transvaginal evaluation is done, the fact that the clinician's hand to be used for simulation of fetal situs changes and this situation may lead to difficulties. An important advantage of the clock position method is that the practitioner does not have

Table 1. Demographic characteristics of cases

Age (years)	30 (23-36)
Gestation (weeks)	30+0 (26+2-33+6)
Gravidity	3 (1-4)
Parity	0 (0-3)
Presentation	
Vertex	18 (58.1%)
Breech	8 (25.8%)
Transverse	5 (16.1%)
Age, gestation week, gravidity and parity: Median (25^{th}-75^{th} percentile) Presentations: Number (percentage %)	

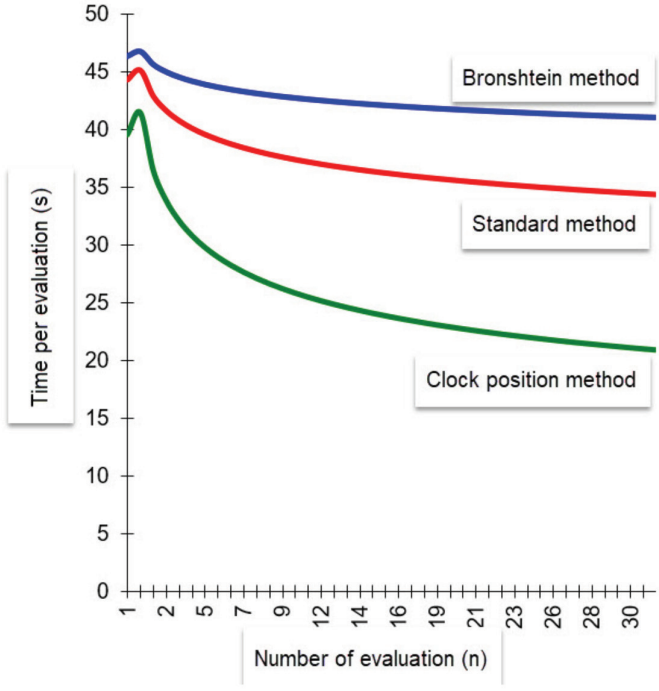

Figure 1. Learning rate curves of three methods

Table 2. Comparison of fetal heart axis evaluation times of three methods

Time (s)	Standard method	Bronshtein method	Clock position method	p
Observer 1				
Vertex (n=18)	16 (12-40)	21 (16-42)	14.5 (10-20)*#	**0.001**
Breech (n=8)	36.5 (23-49.5)	34.5 (19-77.5)	15 (10-31)#	**0.01**
Transverse (n=5)	66 (30.5-106.5)	64 (34-97.5)	32 (15-59.5)#	0.07
Total (n=31)	23 (16-52)	26 (18-49)	16 (10-21)*#	**<0.001**
Observer 2				
Vertex (n=18)	20 (14-35)	32 (25-42)	14 (10-25.5)#	**0.001**
Breech (n=8)	33.5 (12.5-53.5)	41.5 (23-74.5)	16 (11-25)#	**0.028**
Transverse (n=5)	51 (19.5-63)	45 (40.5-94.5)	34 (15-43.5)#	**0.041**
Total (n=31)	21 (14-46)	40 (27-47)*	15 (10-27)*#	**<0.001**
Overall (n=62)	23 (15-47)	35.5 (19-47.5)*	15.5 (10-25.5)*#	**<0.001**
*: p<0.05 when compared with standard method, #p<0.05 when compared with Bronshtein method				

to simulate the fetal position. Mentally conjuring an imaginary clock dial on the fetus is sufficient for the application. Another advantage of the clock position method over the Bronshtein method is that in case the method is forgotten, it is very simple to determine the heart direction according to the fetal situs and then to remember the clock position method. In the Bronshtein method, however, description of the technique should be read again in order to remember the method. Finally, in cases where the fetus is in a vertex presentation, the clinician's arm must be in hyperflexion and forearm must be adjusted according to the back of the fetus while simulating the fetus via the Bronshtein method. This may not be ergonomic for the clinician in some fetal positions. In addition, it may not be appropriate for the clinician to use one arm in this way in front of the patient.

The ease of learning the clock position method is also an important advantage. The challenges experienced by a clinician who has just started residency training are many. In this process, teaching some basic information in a way that is easier to learn renews the residents' self-confidence and enables them to gain practical thinking skills. In addition, the clock position method continues to be easily applicable, not only during the learning phase but also after it is actively used. For all these reasons, we believe that the application of the clock position method in institutions that provide residency training is beneficial.

Study Limitations

This study has strengths and limitations. Prospective design, including residents who do not know fetal heart evaluation, predicting possible bias scenarios to plan the evaluation phase and starting the study by calculating sample size can be listed as strengths. A sample of only two inexperienced residents is the major limitation. Furthermore, due to the small number of patients, fetuses with transverse situs and the low incidence of dextrocardia were also limitations. There is a need for much larger prospective studies to confirm these findings and to validate the clock position method.

Conclusion

We believe that the clock position method is an easy and feasible method for determining the fetal heart axis for inexperienced resident physicians in terms of learning and application.

Ethics Committee Approval: *This prospective study was performed in a single clinic, between September and October 2021, and approved by the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital Local Ethical Committee (approval number: 78, date: 28.04.2021).*

Informed Consent: *Informed consents were obtained from all participants.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Surgical and Medical Practices: C.T., R.A., H.Ü.; Concept: F.A.; Design: F.A., E.V.; Data Collection or Processing: C.T., R.A., H.Ü.; Analysis or Interpretation: E.V.; Literature Search: F.A.; Writing: F.A., B.Y., S.D.*

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

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

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The percentage of peripheral eosinophils as a sensitive marker for differentiating FIGO grade in endometrial adenocarcinomas

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Abstract

Objective: Studies on eosinophils have mostly been directed to parasitic infections and allergic diseases, but the role of eosinophils in oncology has been largely ignored. Eosinophils are an important modulator of the immune response and components of the inflammatory process against the tumor. This study was performed to investigate the pre-operative peripheral blood eosinophil percentages in patients with a histopathologically diagnosed pure endometrioid type endometrial carcinoma.

Material and Methods: Patients' data were analyzed in two groups as present/absent according to whether there are tumor metastases in the adnexes, lymph nodes, cervical stroma, and whether there was lymphovascular space invasion. FIGO grade was taken as the basis of the tumor grade: Low-grade equated to grade 1 or 2, and high-grade equated to grade 3. The requirement for lymph node dissection was based on the Mayo criteria.

Results: The data of a total of 268 patients were included. The mean percentage of eosinophils in high-grade patients (n=29) was 2.75±0.35, and was significantly higher than the mean percentage of eosinophils of found in low-grade patients (n=239), which was 1.79±0.09 (p=0.013). Receiver operator curve analysis showed that a cut-off eosinophil percentage of 1.95% resulted in a sensitivity of 62% and specificity of 67% (p=0.004).

Conclusion: Eosinophil percentages, which are a simple, easily accessible, and inexpensive can be an important pre-operative predictive tool. Eosinophil percentages can be used in determining the need for surgical staging in endometrial cancer. (J Turk Ger Gynecol Assoc 2022; 23: 99-105)

Keywords: Endometrial adenocarcinoma, eosinophil counts, fertility-sparing, tumor grade, peripheral blood eosinophils

Received: 20 October, 2021 **Accepted:** 09 March, 2022

Introduction

Studies on eosinophils, derived from the myeloid series, have mostly concentrated on this cell type's role in parasitic infections and allergic diseases, and the role of eosinophils in oncology has been largely ignored. However, eosinophils are one of the basic cells types of the immune system, like neutrophils and lymphocytes. Studies report that eosinophils are an important modulator of the immune response and components of the inflammatory process against tumors (1,2). In particular, it has been shown that eosinophils can infiltrate the tumor in response to therapeutic agents. In addition, eosinophils have been shown that, as one of the main elements of the tumor microenvironment, they can recognize various stimuli coming from the tumor, synthesize various substances, and direct tumor biogenesis. In this context, eosinophils may contribute to the development of new treatment strategies (3).

The increase in the growth rate and aggression of the tumor directly affects the tumor microenvironment and regulates the immune response through various cytokines, some of which will be produced by the intratumoral eosinophil population. The

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Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2022.2021-9-10

importance of eosinophils, which can be easily and cheaply evaluated using modern laboratory automated hematology analyzers in peripheral blood analysis, has been reported for different types of cancer, including colon and nasopharyngeal cancer (4,5). Furthermore, the importance of eosinophils has been discussed in recent studies in patients with melanoma and lung cancer treated with immunotherapy (6-8), while the role of peripheral blood eosinophils in low and high-grade gliomas has been analyzed very recently (9). Although the role of eosinophils in gynecological tumors has been discussed in relation to cancer of the ovary (10) and cervix (2), there is a limited number of studies in endometrial carcinoma (EC) (11). The aim of the present study was to evaluate pre-operative peripheral blood eosinophil counts and post-operative prognostic factors in patients with endometrioid type EC.

Material and Methods

This retrospective study examined the data, including pre-operative peripheral eosinophil percentages, of patients whose final pathology result was reported as a pure endometrioid type EC. Patients attended between 2014 and 2020. Written and oral informed consent was obtained from all patients before surgery. The study was approved by the University of Health Sciences Turkey, Zeynep Kamil Women and Children Diseases Training and Research Hospital Local Ethics Committee (approval number: 2021/86).

The patients were divided into two groups, based on percentage of the myometrium infiltrated by the tumor (<50% and ≥50%), the presence or absence of tumor metastases in the adnexes, lymph nodes, and cervical stroma, and whether there was lymphovascular area invasion (LVSI) and the data of the two groups was compared. Tumor size (mm) was based on the largest diameter stated in the final pathology report. FIGO grade was used as the basis for evaluation of the tumor grade: low-grade equated to grade 1 or 2, and high-grade equated to grade 3. The requirement for lymph node dissection was based on the Mayo criteria. These were: lymph node dissection was not required in cases of ≤2 cm tumor size (TD), <1/2 myometrial invasion (MI), and low-grade tumors (12). Otherwise, patients with adequate lymph dissection were included in the study, and adequate lymph dissection was defined as the removal of at least 15 pelvic and/or paraaortic lymph nodes (13,14). All patients were re-evaluated in the gynecologic oncology multidisciplinary team meeting before anesthesia examination. As a clinic practice, the maximum acceptable period of approval obtained by consultation is 4 weeks. The percentage of eosinophils in peripheral blood analysis, performed during the pre-operative anesthesia consultation, was used for analysis to standardize and reduce the tendency for variability. Complete blood count analyzes were performed within 4 hours after collection of blood samples into potassium EDTA tubes on a Mindray BC-6800 hematology analyzer. Eosinophil percentages were derived by dividing the eosinophil count by white blood cells (WBC) and multiplying by 100 [(eosinophil/WBC) x100)]. Twenty-seven patients who required lymph dissection but were not staged, 19 patients who were insufficiently staged, and four patients without pre-operative peripheral blood analysis were excluded from the study. All inclusion and exclusion criteria are presented in Figure 1. A further analysis was performed to evaluate the aging factor in EC in terms of tumor grade and eosinophil percentages.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) software, version 20 (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. Histogram and normality plots and Shapiro-Wilk normality test were used for data distribution analysis. Parametric tests were used to analyze continuous variables with normal distribution. A $p<0.05$ was interpreted as significant. Receiver operating characteristic (ROC) analysis was used to determine the threshold value and diagnostic utility of the variables.

Results

A total of 268 patients, with ages ranging from 26 to 82 years, were included. Among these patients, 239 patients with FIGO grade 1 or 2 were defined as low-grade and 29 patients with FIGO grade 3 as high-grade. The mean percentage of eosinophils in high-grade patients was 2.75±0.35, which was

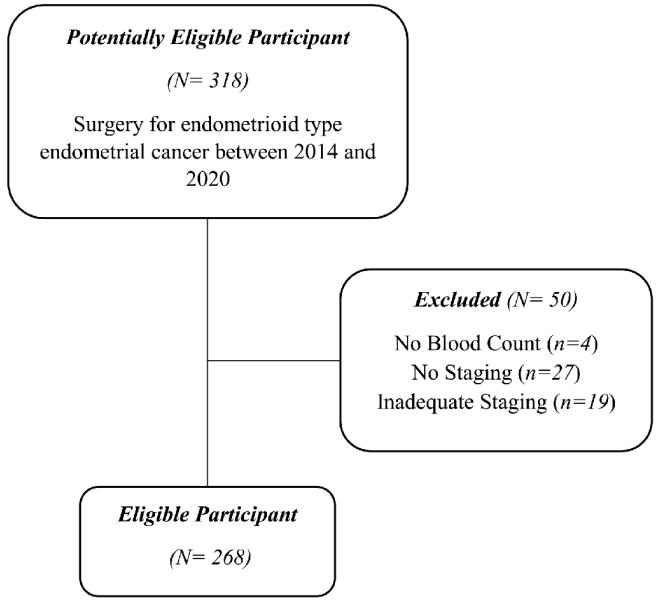

Figure 1. Flow diagram of the study

significantly higher than the mean percentage of eosinophils of 1.79±0.09 found in low-grade patients (p=0.013).

The mean percentage of eosinophils in patients with lymph node metastasis was 2.43±0.34, and tended to be greater than the mean percentage of eosinophils in the group without lymph node metastasis (1.84±0.1). Although this was not significant it was approaching significance (p=0.066). There was no difference in the mean eosinophil percentage of 102 (38.1%) patients with tumor size ≤2 cm (1.89±0.16) and 166 (61.9%) patients with >2 cm diameter tumors (1.90±0.12; p=0.940). The mean percentage of eosinophils of 184 (68.7%) patients with MI ≤1/2 was 1.94±0.11, and the mean percentage of eosinophils of 84 (31.3%) patients with >1/2 was 1.79±0.17 (p=0.464). When the patient groups were compared according to LVSI, cervical stromal invasion, and adnexal involvement, there was no statistically significant difference in terms of the mean percentage of eosinophils. When the patients were separated according to FIGO stages, there was no statistically significant difference in the mean percentage of eosinophils. All detailed statistical analysis results are given in Table 1.

The percentage of eosinophils predicting high-grade tumors with the highest sensitivity and specificity was investigated. In the ROC analysis, when the eosinophil percentage cut-off was taken as 1.95%, the sensitivity was 62% and specificity as 67%. ROC curve analysis was significant (p=0.004) and the area under the curve (AUC) was 0.66 (Figure 2A). When the patients were divided into two groups with eosinophil percentages <1.95% and ≥1.95%, the percentages of high-grade in these groups were 6.5% (11/170) and 18.4% (18/98), respectively. Also, a subgroup analysis was performed in FIGO-stage-1A. Using the ROC curve cut-off eosinophil percentage cut-off of 1.95% in ROC curve analysis yielded an improved sensitivity of 80% and specificity of 65%, which was again significant (p=0.006) with an AUC of 0.76 (Figure 2B).

In further analysis, the mean eosinophil percentages in patients <65 (n=217) and >65 (n=51) years old, were 2.15±0.26 and 1.83±0.09, respectively. There was no significant difference (p=0.273). In addition, age was evaluated in low-grade (n=239) and high-grade (n=29) patients, and the mean age were 56.2±0.59 and 57.86±1.78, respectively, which did not differ (p=0.375) (Figure 3).

The power analysis of the study was calculated using OpenEpi-Power for Comparing Two Means Calculator at www.openepi.com. The mean percentage of eosinophils of the low-grade and high-grade groups was calculated as 74.4% at a 95% confidence interval with ± standard deviation values.

Discussion

Although EC generally appears to have a favorable prognosis, studies have begun to investigate risk factors that may have an impact on survival, besides conventional risk factors (15). Systemic inflammatory biomarkers play an important role in both tumor biogenesis and tumor response. However, the role of eosinophils has long been overlooked in this field. The most striking observation to emerge from our data was that a higher percentage of eosinophils were associated with high-grade tumors in patients with pure endometrioid type EC, which may have promise in terms of predicting pre-operative tumor grade. Tumor-associated leukocytosis (TRL) is defined as the increase in the number of circulating leukocytes without the presence of any infectious condition during malignant disease, which is reported in approximately 10% of cases, excluding

Table 1. Mean percentages of peripheral blood eosinophils according to pathology-related characteristics (n=268)

	n (%)	Mean eosinophils (% ± S.E)	p
Tumor size	-	-	0.940
≤2 cm	102 (38.1)	1.89±0.16	-
>2 cm	166 (61.9)	1.90±0.12	-
MI	-	-	0.464
≤½	184 (68.7)	1.94±0.11	-
>½	84 (31.3)	1.79±0.17	-
FIGO grade	-	-	**0.013**
Low	239 (89.2)	1.79±0.09	-
High	29 (10.8)	2.75±0.35	-
LVSI	-	-	0.413
No	179 (66.8)	1.87±0.11	-
Yes	89 (33.2)	1.95±0.17	-
Cervical stromal invasion	-	-	0.921
No	250 (93.3)	1.90±0.10	-
Yes	18 (6.7)	1.86±0.32	-
Adnexal involvement	-	-	0.721
No	261 (97.4)	1.90±0.09	-
Yes	7 (2.6)	1.69±0.50	-
Lymph node metastasis	-	-	0.066
No	243 (90.7)	1.84±0.10	-
Yes	25 (9.3)	2.43±0.34	-
FIGO stage	-	-	0.566*
1	226 (84.3)	1.85±0.10	-
2	9 (3.4)	1.82±0.27	-
3	25 (9.3)	2.30±0.34	-
4	8 (3.0)	2.07±0.64	-

n: Number, %: Percent, S.E: Standart error, FIGO: The International Federation of Gynecology and Obstetrics, Low-grade: Defines FIGO grade 1 and 2, High-grade: Defines FIGO-grade-3, MI: Myometrial invasion, LVSI: Lymphovascular space invasion. Statistical analyses were obtained by Independent samples t-test (*: Obtained by One-Way ANOVA).

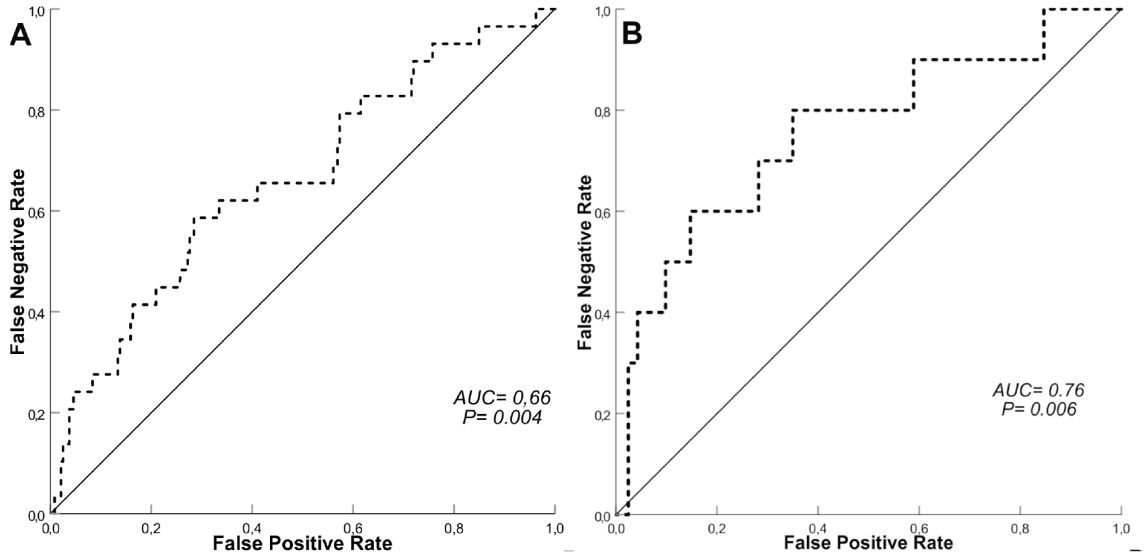

Figure 2. A) Receiver operating characteristic (ROC) curve analysis of mean eosinophils percentages regarding high-grade tumors (cut-off: 1.95%, sensitivity: 62%, specificity: 67%). B) ROC analysis of mean eosinophils percentages regarding high-grade tumors in FIGO-stage-1A (cut-foff: 1.95%, sensitivity: 80%, specificity: 65%)

AUC: Area under the curve

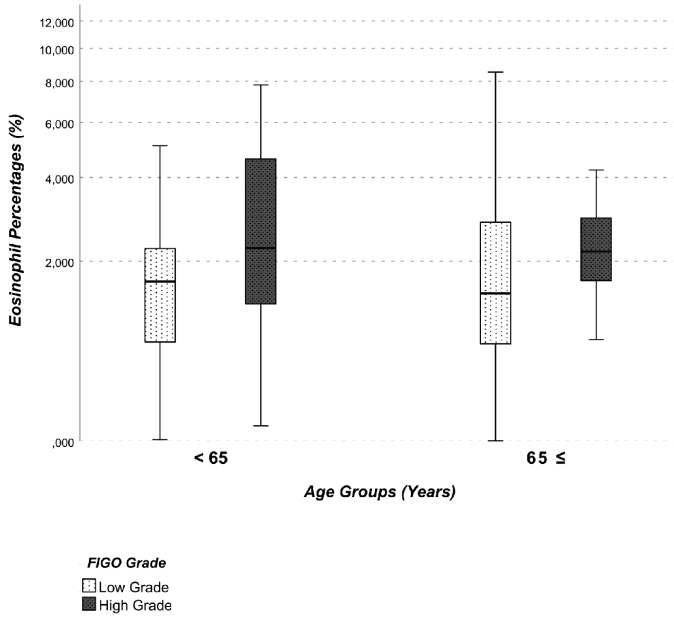

Figure 3. The mean percentages of eosinophils in low-grade and high-grade patients according to age groups (<65 and ≥65) (p=0.273)

FIGO: International Federation of Gynecology and Obstetrics

hematopoietic malignancies (16). However, studies on cervical cancer have reported higher rates of TRL in patients with larger tumor size, advanced stage, a greater number of lymph node metastases, and poorer response to radiotherapy (17). These results are interpreted as leukocytosis, which is evidence of advanced disease, and has a negative impact on the prognosis (18). It has been shown that the response to chemotherapy in breast cancer is associated with immune cells in the peripheral blood (19). A lower eosinophil count is associated with worse survival outcomes in hepatobiliary cancer (20). Similarly, low eosinophil counts were recently found to be associated with worse survival in melanoma (21). Conversely, blood eosinophilia may be the result of tumor necrosis and it may indicate advanced disease. Inflammation caused by necrosis leads to eosinophilia related to poor prognosis (22,23). In addition, prostaglandins (PG), which are important lipid building blocks of the body and important mediators of systemic responses, play an important role in tumor immunology (24). Particularly, PG-E2 which is secreted by eosinophils, weakens antigen presentation by creating an immunosuppressive microenvironment resulting in inhibition of T-cell activation (25). Apart from this, eosinophils can accelerate the disruption of the extracellular matrix. Briefly, the role of blood eosinophils in gynecological tumors has not yet been clarified. Thus the aim of this study was to examine the role of eosinophils in EC.

In the presented study, patients with pure endometrioid histopathology were enrolled to evaluate the analysis in a histopathologically homogeneous cohort. Although the percentages of the eosinophils according to MI (≤1/2, >1/2), TD (≤2 cm, >2 cm), LVSI (yes/no), cervical stromal invasion (yes/no), adnexal involvement (yes/no), lymph node metastasis

(yes/no) and FIGO stages did not show a significant difference, in the high-grade tumors there was a significantly higher percentage of peripheral eosiniphils which may be promising in terms of predicting pre-operative grade. Since the possibility of lymph node involvement is significantly increased in high-grade tumors, staging is required regardless of other factors (12). The addition of information about peripheral eosinophil percentages may provide more supporting evidence when informing the patient about whether to perform staging, should the findings of this study be supported by more evidence.

In a subgroups analysis, we evaluated whether patient age would have an effect on tumor grade and, in particular, on eosinophil percentages. There were no significant differences, so it was accepted that age variability did not affect the main results of this study. A further confounder may have been the fact that we only analyzed endometrioid-type EC. Multiple factors can unintentionally change the WBCs and thus the eosinophil count. Even non-steroidal anti-inflammatory drugs can affect this (26,27). The percentage of eosinophils was calculated to be higher in male participants (compared to female) and <18 years of age (compared to ≥18 years old) in a study conducted with 11,000 patients (28). As our study is based in female oncology patients, all older than 18 years, these possible confounding factors can be ignored. Immune function changes with aging. Aging does not change the chemotaxis or adhesion of eosinophils but may cause a decrease in degranulation (29). However, there is no current evidence to suggest an increase in eosinophil count as an individual ages, consistent with this study (30).

The 5-year survival rate in endometrioid type EC has been reported to be 90.3% in stage 1A (31). It is also quite reasonable for stage 1A patients who died in 5 years to be FIGO-grade-3 endometrioid EC. This situation is more important in young patients who wish to remain fertile. Since EC is seen even at a very young age, even as young as as 13 years, this is of concern in young patients with a desire to have children (32). The main treatment for EC is hysterectomy, but grade becomes the most important parameter in patients who desire fertility preservation and are considered to be stage 1A by imaging methods (33). Unfortunately, the probe curettage (PC) to predict FIGO grade has low power, which also often depends on experience (34,35). In this context, pre-operative blood eosinophil percentages may be a guide to patient selection and risk determination. The combined use of PC-FIGO grade and pre-operative eosinophil percentages in grade determination may show higher accuracy values. Models created with a parameter containing both can be planned as fertility-sparing surgery is not recommended for high-grade tumors, even in younger patients. For this reason, a subgroup analysis was also performed in our patients who were reported to be stage 1A. We found that the sensitivity and specificity of percentages of eosinophils in stage 1A patients were even better in predicting high-grades. Patients with cervical stromal involvement, deep MI, lymph node involvement, or distant metastasis may be exposed to confounding immunological factors that we cannot explain, simply in terms of peripheral blood eosinophil analysis. However, the present study, which was completed with a homogeneous cohort and large number of patients, may be reassuring for the grade confirmation of patients who desired fertility.

Socio-demographic characteristics of the population were not taken into account and eosinophils can be affected by multiple factors, including lifestyle. Undiagnosed comorbidities, such as diabetes, allergy or inflammatory diseases, would affect the peripheral eosinophil percentage either by affecting the eosinophil count directly or by changing the ratio of eosinophils to other leukocytes. In addition, the role of coexistant chronic diseases and dietary habits remain unclear. Thus, adjustment for, sociodemographic variability may provide an even more homogenous study population, but this was not taken into account in the present study. There were several other limiting factors. A high-grade tumor was present in 10.8% of the patients. Also, there is an association between lymph node involvement and the percentage of eosinophils, but this did not reach statistical significance. Further large-scale studies may help to determine this possible association. Moreover, this study only contained endometrioid type EC, which is known to have a better prognosis than other histological subtypes. So, the absence of possible confounding factors allowed us to give a clearer result. But, the role of blood eosinophils can show less stature in EC than the other cancers. In this regard, the percent of high-risk patients in the study population, can change this significance and prognostic factors status. In addition, progression-free survival and overall survival could not be assessed in this study of the prognostic significance of eosinophils. However, almost all studies involving biomarkers of systemic inflammation are retrospective study designs (6,16,21). The results of this study need to be supported by further larger studies.

Conclusion

A statistically significant correlation was found between pre-operative percentages of peripheral blood eosinophils and tumor grade. Eosinophil percentages, which are simple, easily accessible, and inexpensive, may have use as a predictive tool in determining the need for pre-operative and intra-operative surgical staging in EC.

Ethics Committee Approval: *The study was approved by the University of Health Sciences Turkey, Zeynep Kamil Women*

and Children Diseases Training and Research Hospital Local Ethics Committee (approval number: 2021/86).

Informed Consent: *Written and oral informed consent was obtained from all patients before surgery.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Surgical and Medical Practices: S.A., M.A., C.K.; Concept: S.A., U.K.Ö., M.A.; Design: S.A., U.K.Ö., E.K., M.A., C.K.; Data Collection or Processing: S.A., U.K.Ö., E.K., C.M.A.; Analysis or Interpretation: S.A., U.K.Ö., C.M.A.; Literature Search: S.A., U.K.Ö., E.K., C.M.A.; Writing: S.A., U.K.Ö., E.K., C.M.A., M.A., C.K.*

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

Financial Disclosure: *This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.*

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A novel marker endoplasmic reticulum to nucleus signalling-1 in the diagnosis of gestational diabetes mellitus

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Abstract

Objective: We aimed to investigate maternal plasma endoplasmic reticulum to nucleus signalling-1 (ERN-1) concentrations in patients diagnosed with gestational diabetes mellitus (GDM).

Material and Methods: This was a cross-sectional study of 57 pregnant women with GDM and 40 gestational age- and body mass index-matched, healthy pregnant controls, conducted between August 2020 and November 2020. Plasma ERN-1 levels, other laboratory markers of insulin resistance, and demographic characteristics were compared between groups.

Results: Fasting glucose, insulin, homeostasis model assessment of insulin resistance (HOMA-IR), hemoglobin A1c and plasma ERN-1 levels were significantly higher in the GDM group than in the healthy controls ($p<0.001$). Positive correlation was found between ERN-1 levels and HOMA-IR values ($p=0.016$). The optimal cut-off value for ERN-1 to diagnose GDM was 6.960 ng/mL, with a sensitivity of 78.9% and a specificity of 75.0% ($p<0.001$).

Conclusion: ERN-1 may be considered as a new marker for diagnosis of GDM and may also be a potential target in studies of GDM treatment modalities. (J Turk Ger Gynecol Assoc 2022; 23: 106-10)

Keywords: Endoplasmic reticulum stress, endoplasmic reticulum to nucleus signalling-1, getational diabetes mellitus, unfolded protein response

Received: 30 September, 2021 **Accepted:** 21 December, 2021

Introduction

Gestational diabetes mellitus (GDM) is traditionally described as abnormal glucose tolerance with onset, or noticed for the first time, in the course of gestation (1,2). GDM develops when pancreatic ß-cells insulin secretion is unable to compensate for physiologic insulin resistance of pregnancy because of impaired ß-cell function (3-5). Although it differs based on the population characteristics and diagnostic criteria, GDM is a complication that occurs in about 6-7% of pregnancies. However, it is known that the frequency of GDM has tended to increase in the last years because of the increasing trends in the average maternal age and obesity (6-8). GDM with uncontrolled blood glucose levels can lead to some complications for the mother and baby, including macrosomia, shoulder dystocia, birth trauma, preeclampsia, cesarean delivery, neonatal hyperbilirubinemia, and hypoglycemia (9-11). These women are also at increased risk of developing type 2 diabetes, cardiovascular disease, and metabolic syndrome in the future. Furthermore, children born to a woman with GDM have increased risks for obesity and diabetes later in life (12).

Increasing evidence suggests that endoplasmic reticulum (ER) stress is strongly related to the pathogenesis of diabetes. The ER is an organelle in which newly synthesized secretory proteins

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Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2021.2021-9-28

are folded and assembled. Peripheral insulin resistance can induce pancreatic ß-cells to increase production of proinsulin. Overproduction of proinsulin leads to excessive unfolded or misfolded proinsulin accumulation in the ER. When this accumulation becomes intolerable, ß-cell toxicity death occurs. This is known as ER stress. In an attempt to ameliorate the ER stress, a defense system known as the "unfolded protein response" (UPR) is activated in ß-cells (13-15). UPR signaling is regulated by three main molecules: endoribonuclease inositol-requiring protein-1α (IRE-1α); activating transcription factor-6; and protein kinase RNA-like endoplasmic reticulum kinase (16). IRE-1α is encoded by the *ERN-1* gene in humans and is also known as ER to nucleus signalling-1 (ERN-1). Since the pathophysiology of GDM is similar to type 2 diabetes, we hypothesized that ERN-1 levels may be altered in patients with GDM, secondary to increased ER stress and UPR activation.

In this study, we investigated circulating levels of ERN-1 in patients with GDM and compared these with healthy pregnant controls. To the best of our knowledge, this is the first study to examine circulating levels of ERN-1 and its utility in the diagnosis of GDM.

Material and Methods

Patient selection

This cross-sectional study was performed in the Perinatology outpatient clinic of the University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital, between January 2020 and May 2020. The study was approved by the University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital Clinical Research Ethics Committee (approval number: KAEK/2020.07.159). Written informed consent was obtained from all participants.

Singleton pregnant women between 24 and 28 gestational weeks were eligible for participation. The GDM group consisted of pregnant women diagnosed following an oral glucose tolerance test (OGTT) while the healthy control group of randomly selected gestational week- and body mass index (BMI)-matched healthy pregnant women had normal results on OGTT. GDM screening was performed with a 75 g OGTT in all participants. According to the International Association of Diabetes and Pregnancy Study Groups criteria, GDM was diagnosed if at least one of the following plasma glucose levels (fasting ≥92 mg/dL, 1 hour ≥180 mg/dL, 2 hour ≥153 mg/dL) were obtained (1). In patients diagnosed with GDM, diet modification was made and insulin therapy was started, if necessary.

Patients who had pre-existing diabetes mellitus, chronic hypertension or gestational hypertensive disorders, and multiple gestation were excluded.

Blood sampling

Fasting venous blood samples were taken from patients to analyze ERN-1 concentrations. After clotting, the samples were immediately centrifuged at 3000 rpm for 10 minutes. Serum was separated and stored at -80 °C until analysis. A commercial ELISA kit was used for the quantitative analysis of ERN-1 levels (Mybiosource Inc., San Diego, CA, USA. Catalog No: MBS1603218).

For secondary comparative analyses, insulin and hemoglobin A1c (HbA1c) concentrations were analyzed. The homeostatic model assessment of insulin resistance (HOMA-IR) values were calculated with the following equation: fasting glucose (mmol) x fasting insulin (lU/mL)/22.5.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 20.0 (SPSS Inc., Chicago, IL, United States). Kolmogorov-Smirnov and Shapiro-Wilk tests were used to analyze the distribution of continuous variables. The Levene test was used to analyze the homogeneities of variances. Chi-square and/or Fisher's exact test for categorical variables and Student's t-test or Mann-Whitney U test for continuous variables were used to evaluate differences between groups. Correlations between variables and ERN-1 were evaluated by Spearman's correlation coefficient and related p-values. ERN-1 cut-off value was estimated by using the index of Youden. A $p<0.05$ was considered as statistically significant. Post-hoc analysis was conducted for ERN-1, which was determined as the primary outcome variable of the study, in order to find a statistically significant difference of approximately 20% between the control and GDM groups means, for which the sample size was calculated according to the F-test with 0.05 error level and minimum 80% power. The sample size was found to be 90.

Results

We included a total of 97 singleton pregnant women, of whom 57 (58.8%) were diagnosed with GDM and the remaining 40 (41.2%) were controls with normal OGTT results. Among the 57 women with GDM, while glycemic control could be achieved in 35 (61.4%) by diet, insulin therapy was started in 22 (38.6%) of them. Demographic features and clinical outcomes of patients with GDM and healthy controls are shown in Table 1. There was no significant difference between the groups in terms of maternal age, height, weight, BMI, gestational week at sampling, gestational week at birth and birth weight. Biochemical parameters of the two groups are presented in Table 2. Fasting Glucose, insulin, HbA1c, HOMA-IR and ERN-1 variables were compared between the GDM and control group

and all were significantly higher in the GDM group compared to the control group (all; p<0.001).

Correlations between maternal ERN-1 levels and other clinical or biochemical variables were analyzed. No correlation was observed with any parameter other than HOMA-IR where there was a positive correlation with ERN-1 levels (r=0.329, p=0.016; Table 3).

According to the receiver operating characteristic analysis, ERN-1 level was a statistically significant parameter to predicting GDM. The cutoff value was 6.960 ng/mL for the diagnosis of GDM with a sensitivity of 78.9% and a specificity of 75.0% (p<0.001) (Figure 1).

Discussion

In this study, the plasma ERN-1 levels, demographic characteristics and biochemical parameters of women with GDM and normoglycemic pregnant controls were compared. ERN-1 concentrations in patients with GDM were significantly higher than those of the healthy control group. Furthermore, serum ERN-1 concentrations were significantly positively correlated with HOMA-IR values. HOMA-IR values are derived from measurements of fasting insulin and fasting glucose values but, interestingly, the only correlation identified was between ERN-1 and the final HOMA-IR value while no correlation was observed with fasting insulin and fasting glucose. We suggest that plasma ERN-1 concentrations may be a novel and predictive parameter for GDM.

The pathogenesis of diabetes is not completely understood but growing evidence suggests that, during progression of disease, loss of pancreatic ß-cell function and ultimate loss of ß-cell mass is accompanied by ER stress (13-15). Pancreatic ß-cells increase proinsulin production as a result of insulin-resistant peripheral tissues. The ER protein-folding mechanisms may be overwhelmed with the excess production of proteins, including proinsulin, translocated into the ER, resulting in ER stress. These unfolded proteins aggregate in the ER and activate downstream signaling mechanisms, which has been called the UPR (16). The UPR leads to protein translation attenuation and also triggers a mechanism to remove misfolded protein from the ER, which has been termed ER-associated degradation (17). IRE-1 acts as an ER stress sensor of unfolded proteins in the ER and triggers UPR. ERN-1 protein is a human homologue of the IRE-1.

Type 2 diabetes and GDM have similar physiopathological mechanisms, notably insulin resistance. Therefore, we hypothesized that ERN-1 concentrations may increase in the course of GDM, as they do in type 2 DM, secondary to increased ER stress and UPR. This study has demonstrated that ERN-1 concentrations were substantially increased in patients with GDM and provided evidence that increased ER stress may also perform a role in the pathophysiology of GDM, similar to type 2 diabetes.

Conclusion

This study is the first to report that maternal ERN-1 levels are significantly higher in patients with GDM than in healthy, gestational week- and BMI-matched pregnant women.

Table 1. Demographic features and clinical outcomes of the groups

	GDM group (n=57)	Control group (n=40)	p
Age (years)	32.40±6.15	30.62±3.79	0.108*
Maternal height (cm)	161.03±5.70	162.37±4.49	0.219*
Maternal weight (kg)	74.14±10.94	71.80±6.14	0.564
Body mass index (kg/m^2)	28.52±3.80	27.21±1.86	0.158
Gestational week at sampling	27.43±3.33	26.35±2.60	0.060
Gestatioanl week at birth	38.77±2.764	39.12±2.20	0.588
Birth weight (g)	3226.70±721.95	3254.55±346.03	0.424
*Asterisked p-values refer to p-values from Student's t-test, others to Mann-Whitney U test. GDM: Gestational diabetes mellitus			

Table 2. Biochemical parameters of women diagnosed with GDM and the control group

	GDM group (n=57)	Control group (n=40)	p
Fasting glucose (mg/dL)	95.36±13.26	80.20±5.73	**<0.001***
Insulin (mU/L)	12.87±3.04	8.05±1.75	**<0.001***
HbA1c (%)	5.93±0.87	5.05±0.33	**<0.001**
HOMA-IR	3.03±0.80	1.58±0.33	**<0.001**
ERN-1 (ng/mL)	9.70±5.24	6.39±1.53	**<0.001**
*Asterisked p-values refer to p-values from Student's t-test, others to Mann-Whitney U test. GDM: Gestational diabetes mellitus, ERN-1: ER to nucleus signalling-1, HbA1c: Hemoglobin A1c, HOMA-IR: Homeostasis model assessment of insulin resistance			

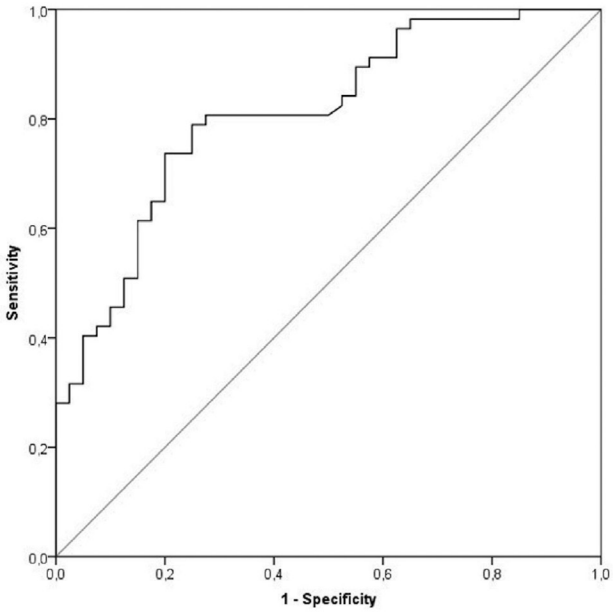

Figure 1. Receiver operating characteristic curve showing the diagnostic utility of ER to nucleus signalling-1 in gestational diabetes mellitus

Table 3. Correlation analyses between ERN-1 concentration and other variables

ERN-1		
	r	**p**
Age	-0.322	0.083
Maternal height	-0.021	0.912
Maternal weight	0.168	0.375
BMI	0.231	0.220
HbA1c (%)	0.033	0.864
Insulin (mU/L)	0.240	0.202
Fasting glucose (mg/dL)	0.047	0.804
HOMA-IR	0.329	0.016
Gestatioanl week at birth	-0.194	0.304
Birth weight (g)	-0.088	0.644
Gestational week at sampling	0.136	0.233

ERN-1: ER to nucleus signalling-1, BMI: Body mass index, HbA1c: Hemoglobin A1c, HOMA-IR: Homeostasis model assessment of insulin resistance

Furthermore, ERN-1 concentration was positively correlated with HOMA-IR. Prompt recognition and management of GDM are essential to reduce the adverse fetal and maternal outcomes and protecting neonates and mothers from long-term complications. The OGTT, which is widely used for screening pregnant women at risk of GDM, is not comfortable and tolerable by many pregnant women. In this context, ERN-1 might be suggested as a potential marker to predict the development of GDM. ERN-1 should also be considered as a potential target for medical intervention in GDM.

Ethics Committee Approval: *The study was approved by the University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital Clinical Research Ethics Committee (approval number: KAEK/2020.07.159).*

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

Peer-review: *Externally peer-reviewed.*

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

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

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

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Can the application of a temporary uterine tourniquet during an abdominal myomectomy reduce bleeding?

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Abstract

Objective: Uterine fibroids are common, benign uterine tumours. The three most common surgical treatment approaches for uterine fibroids are laparoscopic, robotic and abdominal myomectomies. Bleeding is a risk with all three approaches. The present study compared post-operative and pregnancy outcomes in patients with bilateral uterine artery occlusion who underwent an abdominal myomectomy, with or without a temporary uterine tourniquet.

Material and Methods: This retrospective study included patients with intra-mural fibroids (≥5 cm) who underwent an abdominal myomectomy. The patients were divided into two groups according to the use or non-use of a temporary uterine tourniquet. Post-operative and pregnancy outcomes in the tourniquet use and non-use groups were compared. The association of the number of uterine fibroids removed (≤3 vs >3) with laboratory parameters was also evaluated.

Results: A total of 84 patients were included, divided into use (n=36) and non-use (n=48) of the temporary tourniquet. There was a statistically significant difference between the groups with >3 myomas removed and with a uterine tourniquet applied and not applied in terms of reduction in hemoglobin and hematocrit, transfusion amounts, operation times and lengths of hospitalization in favour of the uterine tourniquet use group (p=0.019, p=0.023, p=0.012, p=0.044 and p=0.036, respectively). Bilateral uterine arterial occlusion using a temporary uterine tourniquet had no negative effects on pregnancy outcomes.

Conclusion: A temporary uterine tourniquet may be an effective method for reducing the amount of perioperative bleeding in patients with multiple, large-sized myomas located close to vascular structures. (J Turk Ger Gynecol Assoc 2022; 23: 111-6)

Keywords: Blood loss, leiomyoma, myomectomy, uterine artery occlusion

Received: 06 January, 2019 **Accepted:** 30 April, 2021

Introduction

Uterine fibroids, also known as leiomyomas or myomas, are common, benign uterine tumours. Leiomyomas are detected in 50-60% of women aged 50 years and younger, with the rate increasing after the age of 50 years to 70%. Furthermore, 25% of all leiomyomas will require treatment (1). The uterus has a rich supply of blood vessels. The uterine arteries, branches of the anterior division of the internal iliac artery, are the main source of the blood supplied to the uterus and the only source of vascular supply to uterine fibroids (2,3). As most of the blood that enters the uterus does so through uterine arteries, transient uterine ischemia may occur following occlusion of the arteries using a catheter or tourniquet. Shortly after occlusion of the arteries, blood within the myometrium clots, the myometrium becomes hypoxic, and the metabolic pathway shifts from oxidative metabolism to anaerobic glycolysis. Some hours after occlusion, lysis of blood clots within the myometrium occurs, followed by reperfusion of the uterus through collateral arteries (4).

The three most common surgical treatment methods for uterine fibroid removal are laparoscopic, robotic and abdominal myomectomies (5). Due to the highly vascular nature of uterine fibroids, bleeding is a risk with all three surgical methods (6). Previous research reported mean blood loss in a myomectomy of 150-1,050 mL and a blood transfusion rate of 20% (7). Uterine

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Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2021.2020-0242

bleeding during surgery and intra-operative transfusions may give rise to long-term complications, such as antibodies directed specific for red blood cells, in addition to increased perioperative morbidity and mortality, and may affect the outcomes of future pregnancies (8,9).

The aim of this study was to evaluate the effectiveness of a temporary tourniquet in reducing blood loss in abdominal myomectomy cases and to determine whether bilateral uterine artery occlusion had adverse consequences for future pregnancies.

Material and Methods

This retrospective study was approved by Muğla Sıtkı Koçman University Institutional Review Board Ethics Committee (approval number: 13/II, date: 11.11.2020). All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Prior to undergoing surgery, written informed consent was obtained from all the participants.

Eighty-four patients who underwent an abdominal myomectomy between January 2015 and January 2019 to remove intra-mural myomas of at least 5 cm in diameter, as detected by pre-operative imaging, were included in the study. In all cases, the cytopathological diagnosis was a leiomyoma. The indications for a myomectomy were symptomatic leiomyomas causing pelvic pain and abnormal uterine bleeding, together with symptomatic anaemia and feelings of pressure in the urinary bladder, bowel or pelvic vessels. Patients who underwent a laparoscopic myomectomy, patients aged <18 years, pregnant patients and patients with a cytopathological diagnosis of a malignant myoma or an adenomyoma were not included in the study. The same surgeon performed all the surgeries.

Pre-operative demographic characteristics, and pre- and post-operative laboratory values were obtained from the electronic medical records and patients' files. The demographic characteristics recorded included age, gravida and body mass index. Data on abdominal surgery history, indications for surgery, duration of hospital stay and length of the surgical procedure were also recorded. In addition, pre-operative hemoglobin (Hb) and hematocrit (Hct) values, post-operative 24-hour Hb and Hct values, reduction in the Hb and Htc values between pre-operative and post-operative levels and blood transfusion information were recorded. All the patients were contacted by phone and asked about post-operative symptoms, pregnancies and pregnancy-related outcomes.

The patients were divided into two groups according to the use or non-use of a temporary uterine tourniquet, and the patients' intra-operative and post-operative laboratory and clinical results were compared. In addition, the association between the number of uterine fibroids removed (≤3 and >3) and laboratory parameters in the tourniquet use and non-use groups was analysed.

Surgical technique

A laparotomy was performed with a Pfannenstiel or median incision. Temporary bilateral uterine artery occlusion was performed in patients with multiple myomas, submucous myomas and myomas in close proximity to vascular areas. A Penrose drain was used for temporary uterine artery occlusion. A window with a diameter of 1-2 cm was opened between the bilateral ligamentum latum leaves, and the drain, approximately 20 cm long, was passed through the window. A pericervical ring was formed at the junction of the cervix of the uterus with the Penrose drain. The Penrose drain was tied on the anterior surface of the uterus using at least three surgical knots at the level of the internal cervical os. The myomas were not injected with vasopressin before the myomectomy. At the point where the myoma projected from uterus, an incision was made using monopolar cautery or a scalpel, and the myoma was enucleated. After myoma enucleation, the myometrium was closed using the baseball technique with one or two layers of no: 0 Vicryl® (polyglactin 910, Ethicon, USA) suture. After repair of the myometrium, the Penrose tourniquet was removed using scissors.

Statistical analysis

The data were analysed using the Statistical Package for Social Science (SPSS), version 20.0 for Windows (IBM Corp., Armonk, NY, USA). Summary statistics are given as mean ± standard deviation, median and (minimum-maximum) and percentage. The Independent samples t-test was applied for continuous variables. The Mann-Whitney U test was used for inter-group comparisons of parameters with a non-normal distribution. A chi-square test was used for comparison of categorical data. In all the analyses, a value of $p<0.05$ was considered statistically significant.

Results

Eighty-four patients who underwent laparotomic myomectomy were retrospectively included. The demographic characteristics of the patients in the tourniquet use (n=36) and non-use groups (n=48) were similar (Table 1). There was no statistically significant difference between the two groups in terms of haemorrhages, transfusion needs, operative times and lengths of hospitalization (Table 2). There was also no statistically significant difference in the pre- and post-operative Hb, Htc, Hb reduction and Htc reduction values of the tourniquet and non-tourniquet use groups.

When the patients were evaluated according to the number of uterine myomas removed during the abdominal myomectomy, there was no statistically significant difference in blood loss amount, transfusion needs and lengths of hospitalization in those with ≤3 myomas removed, irrespective of the use or non-use of a tourniquet (Table 3). Post-operative Hb (7.12±1.13 and 9.14±1.21, respectively, p=0.030) and Hct values (22.04±3.54 and 29.01±2.88, respectively, p=0.041) of patients in the non-tourniquet use group with >3 intra-mural myomas removed were significantly lower than those of patients with >3 intra-mural myomas removed in the tourniquet use group. In addition, in the patients with >3 uterine fibroids removed, Hb and Htc drop values were significantly lower in the tourniquet use group as compared to those in the non-use group (p=0.041 and p=0.023, respectively). The transfusion amounts, operative times and lengths of hospitalization were significantly lower in the tourniquet use group compared to the non-use group (p=0.012, p=0.044 and p=0.036, respectively) (Table 3).

Twelve (33%) patients in the tourniquet use group and 17 (35.4%) patients in the tourniquet non-use group reported pregnancy during the post-operative period. The total number of pregnancies in the two groups was similar (p=0.105) (Table 4). Uterine tourniquet use had no adverse effects on pregnancy outcomes in terms of total number of pregnancies, miscarriages, assisted reproductive pregnancies, live births, birth weights, gestational week at birth, and occurrence of stillbirth, uterine rupture or placenta previa.

Discussion

The most common symptoms of myomas, which are sex steroid hormone-dependent benign uterine tumours, are menorrhagia and anaemia. A myomectomy is the most common surgical treatment method for women with symptomatic leiomyomas who wish to retain their uterus and fertility (10). Perioperative bleeding is the most common complication in a myomectomy (6). Previous research reported that the surgery duration and uterine leiomyoma number were risk factors for increased blood loss, with a longer surgery duration and removal of multiple uterine leiomyomas associated with increased blood loss (11). This research also reported that increased myomectomy-related blood loss contributed to delayed post-operative recovery by increasing the need for blood transfusions and the risk of fevers, infections and abdominal adhesions (12).

The present study included 84 patients with intra-mural myomas of ≥5 cm in diameter and a cytopathological diagnosis of leiomyoma who underwent an abdominal myomectomy. In our study, a temporary uterine tourniquet was applied in 43% of the patients. We detected no statistically significant difference

Table 1. The demographic characteristics of the patients

Variables	Without UT (n=36) [a]Mean ± SD [b]Median (minimum-maximum)	With UT (n=48) [a]Mean ± SD [b]Median (minimum-maximum)	p
Age (year)	41 (28-51)	40 (24-48)	0.211[b]
BMI (kg/m^2)	29.86±4.21	27.42±3.43	0.082[a]
Gravidity (n)	2 (1-5)	2 (1-5)	0.253[b]
Myoma size (cm)	7 (5-11)	6 (5-14)	0.482[b]
Number of myomas (n)	3.68±1.39	3.12±1.33	0.121[b]
UT: Uterine tourniquet, SD: Standard deviation, BMI: Body mass index. [a]Independent samples t-test, [b]Mann-Whitney U test			

Table 2. Post-operative outcomes of patients with and without uterine tourniquet application

Variables	Without UT (n=36) [a]Mean ± SD [b]Median (minimum-maximum)	With UT (n=48) [a]Mean ± SD [b]Median (minimum-maximum)	p
Pre-op Hb (g/dL)	9.92±1.14	10.59±1.15	0.115[a]
Post-op Hb (g/dL)	9.08±1.10	8.72±1.38	0.128[a]
Pre-op Htc	30.09±3.15	31.92±3.34	0.098[a]
Post-op Htc	27.77±3.59	26.11±4.12	0.276[a]
Transfusion (units)	0 (0-5)	0 (0-5)	0.071[b]
Operative time (mins)	70 (52-86)	68 (51-80)	0.276[b]
LOH (days)	1 (1-3)	1 (1-3)	0.427[b]
UT: Uterine tourniquet, SD: Standard deviation, Pre-op: Pre-operative, Post-op: Post-operative, Hb: Hemoglobin, Htc: Haematocrit, LOH: Length of hospitalization. Significant at the 0.05 level. [a]Independent samples t-test, [b]Mann-Whitney U test			

in blood loss amounts, transfusion needs or operative times in those with ≤3 myomas removed in the uterine tourniquet use and non-use groups. Previous studies reported that the size of the uterus, duration of the operation and total number and weight of myomas removed may affect the amount of blood loss during a myomectomy (13). In this study, in patients in the non-tourniquet use group with >3 uterine fibroids removed, post-operative Hb and Htc values were significantly lower and Hb and Htc drop values were significantly higher, transfusion amounts were significantly higher, and lengths of hospitalization were significantly longer compared to the same parameters in the tourniquet use group in patients with ≤3 uterine fibroids removed.

Intra-myometrial vasopressin and its analogues, intravenous oxytocin, intravenous or vaginal misoprostol, intra-myometrial bupivacaine and epinephrine and tranexamic acid are commonly used in myomectomies to reduce intra-operative bleeding, although there is no strong evidence that they achieve this goal. However, there is evidence to suggest that a uterine tourniquet reduces bleeding during a myomectomy (14-16). Alptekin and Efe (17) reported a significant difference in blood loss in the no tourniquet use versus that in patients in whom a

Table 3. Association between the number of myomas removed and post-operative outcomes

	Intra-mural myoma number ≤3			**Intra-mural myoma number >3**		
	Without UT (n=32) (38%) [a]Mean ± SD [b]Median (minimum-maximum)	**With UT (n=14) (16%) [a]Mean ± SD [b]Median (minimum-maximum)**	**p**	**Without UT (n=16) (19%) [a]Mean ± SD [b]Median (minimum-maximum)**	**With UT (n=22) (26%) [a]Mean ± SD [b]Median (minimum-maximum)**	**p**
Pre-op Hb (g/dL)	10.77±1.31	10.68±1.22	0.345[a]	9.94±1.08	10.24±1.33	0.101[a]
Post-op Hb (g/dL)	9.91±1.25	9.94±1.38	0.068[a]	7.12±1.13	9.14±1.21	**0.030[a]***
Hb drop	0.86±1.16	0.74±1.18	0.073[a]	2.82±1.05	1.1±1.17	**0.019[a]***
Pre-op Htc	32.02±2.94	31.74±2.06	0.088[a]	30.04±1.85	31.11±3.03	0.221[a]
Post-op Htc	27.30±3.94	27.01±3.25	0.413[a]	22.04±3.54	26.01±2.88	0.041[a]*
Htc drop	4.72±2.85	4.73±2.1	0.113[a]	8.01±3.25	5.1±3.66	**0.023[a]***
Transfusion (units)	0 (0-3)	0 (0-4)	0.098[b]	1 (0-5)	0 (0-4)	**0.012[b]***
Operative time (min)	65 (52-75)	64 (51-73)	0.179[b]	79 (65-86)	71 (63-80)	**0.044[b]***
LOH (day)	1 (1-5)	1 (1-5)	0.421[b]	2 (1-5)	1 (1-5)	**0.036[b]***

UT: Uterine tourniquet, SD: Standard deviation, Pre-op: Pre-operative, Post-op: Post-operative, Hb: Hemoglobin, Htc: Hematocrit, LOH: Length of hospitalization. *Significant at the 0.05 level. [a]Independent samples t-test; [b]Mann-Whitney U test

Table 4. Pregnancy outcomes of patients with and without uterine tourniquet application

	Without UT (n=48)	**With UT (n=36)**	**p**
Total number of pregnancies (n) (%)	17 (35.4%)	12 (33%)	0.105[c]
Spontaneous pregnancies (n) (%)	15 (88%)	9 (75%)	0.084[c]
Post-op average spontaneous gestational age (n) (min-max)	33 (27-38)	31 (26-41)	0.432[b]
Assisted reproductive pregnancies (n) (%)	2 (12%)	3 (25%)	0.267[c]
Miscarriage (n) (%)	3 (17.6%)	3 (25%)	0.195[c]
Live birth (n) (%)	14 (82.4%)	9 (75%)	0.351[c]
Pre-term birth (n) (%)	4 (28.5%)	4 (44.4%)	
Term birth (n) (%)	10 (71.5%)	5 (55.6%)	
Gestational week at birth (week) (n) (min-max)	35 (29-37)	33 (30-38)	0.077[b]
Birth weight (g) (mean ± SD)	2720.42±190.20	2540.38±210.24	0.092[a]
Stillbirth (n)	0	0	-
Uterine rupture (n)	0	0	-
Placenta previa (n)	1	1	-

UT: Uterine tourniquet, SD: Standard deviation, Significant at the 0.05 level. [a]Independent samples t-test, [b]Mann-Whitney U test, chi-square test, min.: Minimum, max.: Maximum

tourniquet (Foley catheter) was applied before a myomectomy, with mean blood loss of 673.8±172.3 mL and 286.4±137.5 mL, respectively. Taylor et al. (18) first applied triple tourniquets at the level of the uterine cervix to ovary propriums, and they then applied a uterine tourniquet only at the level of the uterine cervix in subsequent studies. Similar to our results, they reported that the uterine tourniquet reduced the amount of bleeding, need for erythrocyte transfusions and operative times, particularly in myomectomies of patients with multiple myomas. Using a Foley catheter as a uterine tourniquet in myomectomy cases, Ikechebelu et al. (19) detected a significant decrease in mean blood loss in the tourniquet use group versus that in a non-tourniquet use group. In their study, the mean blood loss in the tourniquet use group was 515.7±292.8 mL versus 756.4±285.7 mL in the tourniquet non-use group, and the erythrocyte transfusion amounts in the two groups were 0.24±0.51 and 1.0±1.14 units, respectively. Kwon et al. (20) investigated blood loss in 168 patients who underwent laparoscopic myomectomies or adenomyomectomies, with or without transient occlusion of the uterine arteries using temporary clips. The mean estimated blood loss was significantly lower in the patients in the temporary uterine artery occlusion group than in the non-occlusion group. In our study, we used a Penrose drain as a uterine tourniquet, elaborating on the effectiveness of the tourniquet used in reducing blood loss amounts/transfusion amounts. The data in our study were consistent with those of Kwon et al. (20).

Although uterine tourniquet application would appear to prolong the duration of the operation, previous studies have reported that the use of a tourniquet reduces the amount of bleeding and actually shortens the duration of the operation (21). In a myomectomy study by Mehdizadehkashi et al. (21), they used a Penrose drain to achieve uterine artery occlusion, protecting the uterine tubes and ovarian arteries. They concluded that the tourniquet did not prolong the operation time or reduce the amount of bleeding. In our study, the operation times in patients with >3 myomas removed were shorter in the uterine tourniquet use group than in the non-tourniquet use group.

A previous study investigated the effects of a uterine Penrose drain tourniquet on ovarian reserve, assessing follicle stimulating hormone and anti-Mullerian hormone values. The authors concluded that the tourniquet had no negative effects on ovarian reserve (21). Another study that focused on the effects of triple and single uterine tourniquets during myomectomies also concluded that tourniquet use had no significant effect on ovarian reserve, as determined by anti-Mullerian hormone levels (22). In a meta-analysis by Sanders et al. of patients who underwent a myomectomy with (n=470) or without (n=219) uterine artery occlusion, the authors detected no between-group differences in the courses of subsequent pregnancies or live birth rates (23). In our study, 12 (33%) patients in the tourniquet use group and 17 (35.4%) patients in the tourniquet non-use group became pregnant during the post-operative period. We detected no difference between the pregnancy outcomes of the patients in the uterine tourniquet use and non-use groups.

Study Limitations

The present study has a number of limitations. The first limitation is clearly the retrospective design of the study. Another limitation is that we used Hb and Hct values to determine the amount of intra-operative and post-operative bleeding. A strength of our study is that we investigated pregnancy outcomes in the uterine tourniquet use and non-use groups.

Conclusion

A laparotomic myomectomy is the most common treatment option for women with symptomatic leiomyomas who wish to retain fertility. Bleeding is the most common complication during a myomectomy. The application of a temporary uterine Penrose drain tourniquet seemed to be effective in reducing the amount of perioperative bleeding, particularly in patients with multiple, large-sized myomas located close to vascular structures. Moreover, the uterine tourniquet did not seem to have adverse effects on pregnancy outcomes. Randomized prospective studies with larger numbers of patients are needed to determine the most effective myomectomy method and the effects of various myomectomy methods on fertility.

Ethics Committee Approval: *The study was approved by the Ethical Committee of the Muğla Sıtkı Koçman University Faculty of Medicine (approval number: 13/II, date: 11.11.2020).*

Informed Consent: *Prior to undergoing surgery, written informed consent was obtained from all the participants.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Surgical and Medical Practices: E.A., B.S., A.A.S.; Concept: E.A., B.S., A.A.S.; Design: E.A., B.S., A.A.S.; Data Collection or Processing: E.A., B.S., A.A.S.; Analysis or Interpretation: E.A., B.S., A.A.S.; Literature Search: E.A., B.S., A.A.S.; Writing: E.A., B.S., A.A.S.*

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

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

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This article will be credited by TMA within the scope of CME/CPD.

Can we accurately diagnose endometriosis without a diagnostic laparoscopy?

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Abstract

Endometriosis is a progressive, estrogen-dependent, chronic inflammatory disease that affects approximately 6-10% of reproductive age women. Patients usually presents with symptoms, such as non-menstrual pelvic and abdominal pain, ovulatory pain, dyspareunia, dysmenorrhea, dyschezia, and/or changes to bowel or bladder function, which can be exacerbated during ovulation or menses. Endometriosis is a leading cause of unexplained infertility, accounting for up to 50-80% of cases. Currently, altered endometrial receptivity and progesterone resistance are some of the leading theories that could explain endometriosis-related implantation failure. In the endometrium, the B-cell chronic lymphocytic leukemia/lymphoma 6 (BCL-6) protein forms a complex that binds to and inactivates regulators of the progesterone pathway, leading to progesterone resistance, aberrant decidualization, implantation failure, and recurrent miscarriages in women diagnosed with endometriosis. Surgical diagnosis consisting of laparoscopy, with or without histologic confirmation, is still considered the gold standard for diagnosis of endometriosis. Development of noninvasive screening and diagnostic tests to accurately identify patients with endometriosis has become increasing popular. A screening test for endometriosis has been developed to detect endometrial BCL-6 overexpression in asymptomatic women with unexplained infertility or recurrent pregnancy loss. Positive endometrial BCL-6 testing has been associated with recurrent miscarriages and poor in vitro fertilization outcomes. When the underlying cause of endometrial inflammation secondary to endometriosis was treated, an improvement in subsequent live birth rates was seen. Endometrial BCL-6 testing has a high positive predictive value that could help physicians and patients undergoing infertility treatment to seek surgical evaluation for endometriosis, to improve their reproductive outcomes. (J Turk Ger Gynecol Assoc 2022; 23: 117-9)

Keywords: Infertility, endometrioma, endometriosis, laparoscopic surgery, ReceptivaDx

Received: 03 February, 2022 **Accepted:** 20 May, 2022

Introduction

Endometriosis is considered a progressive, estrogen-dependent, chronic inflammatory disease that affects approximately 6-10% of reproductive age women, with over 200 million women worldwide estimated to be affected (1). Endometriosis can be found in multiple areas of the human body, with extragenital endometriosis leading to thoracic, genitourinary, gastrointestinal, and/or nervous system dysfunction. Patients usually present with symptoms such as non-menstrual pelvic and abdominal pain, ovulatory pain, dyspareunia, dysmenorrhea, dyschezia, and/or changes to bowel or bladder function, which can be exacerbated during ovulation or menses. Extragenital symptoms can also be seen: shoulder pain associated with diaphragmatic endometriosis; upper abdominal pain with pancreatic endometriosis and lumbar pain with sciatic nerve endometriosis; and chest

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Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2022.2022-2-2

pain, hemoptysis and lung collapse in cases of pulmonary endometriosis (2-5). The severity of symptoms can vary from mild to severe, with up to 25% of women being completely asymptomatic (6). In some patient, the only presenting sign of endometriosis may be unexplained infertility, with multiple failed in vitro fertilization (IVF) treatments causing increased suspicion.

Endometriosis is a leading cause of unexplained infertility, accounting for up to 50-80% of women (7). Infertility caused by endometriosis can be explained by several hypotheses including abnormal utero-tubal transport, ovulatory dysfunction, altered cell-mediated immunity, distorted pelvic anatomy, dyssynchronous oocyte maturation, altered endometrial receptivity and decreased oocyte quality (8). Currently, altered endometrial receptivity and progesterone resistance are some of the leading hypothetical mechanisms that could explain endometriosis-related implantation failure. These hypotheses are based on the need for adequate progesterone levels and endometrial receptor expression for embryo implantation, endometrial stabilization and maintenance of pregnancy and any mechanism that interferes with progesterone signaling can cause implantation failure (9-12).

Endometriosis has been associated with aberrant humoral and cellular immunity (12). B-cell chronic lymphocytic leukemia/lymphoma 6 (BCL-6) is a protein encoded by a proto-oncogene present on chromosome 3 (3q27.3) that stimulates inflammatory cytokines such as interleukin-6 (IL-6), IL-8, and IL-17 in the peritoneal fluid of women with endometriosis. In the endometrium, BCL-6 forms a complex that binds to and inactivates regulators of the progesterone pathway, leading to progesterone resistance, aberrant decidualization, implantation failure, and recurrent miscarriages in women diagnosed with endometriosis (8,10-14).

Surgical diagnosis consisting of laparoscopy, with or without histologic confirmation, is still considered the gold standard for the diagnosis of endometriosis. When endometriomas are involved, this can become difficult, as endometrioma subtypes are treated differently in patients desiring to preserve fertility. Type 1 endometriomas arise from implanted endometrial-like tissue on the ovarian cortex (Figure 1A-C). To minimize adverse effects on ovarian reserve and fertility, these are treated by brushing or washing off the lesions. Type 2 endometriomas arise from functional cysts that are invaded by endometrial-like implants. When less than 50% invasion is involved, excision can be performed successfully without compromising ovarian reserve (15-18).

Development of non-invasive screening and diagnostic tests to accurately identify patients with endometriosis has become increasing popular (14). A screening test for endometriosis called ReceptivaDx (CiceroDx, Huntington Beach, CA, USA) has been developed to detect endometrial BCL-6 overexpression in asymptomatic women with unexplained infertility or recurrent pregnancy loss (19). This test also detects beta-3 integrin expression, a cell adhesion molecule integral to successful implantation (11,13). Positive endometrial BCL-6 testing, defined as an HSCORE >1.4, has been associated with recurrent miscarriages and poor IVF outcomes (13,20,21). When the underlying cause of endometrial inflammation secondary to endometriosis was treated, an improvement in

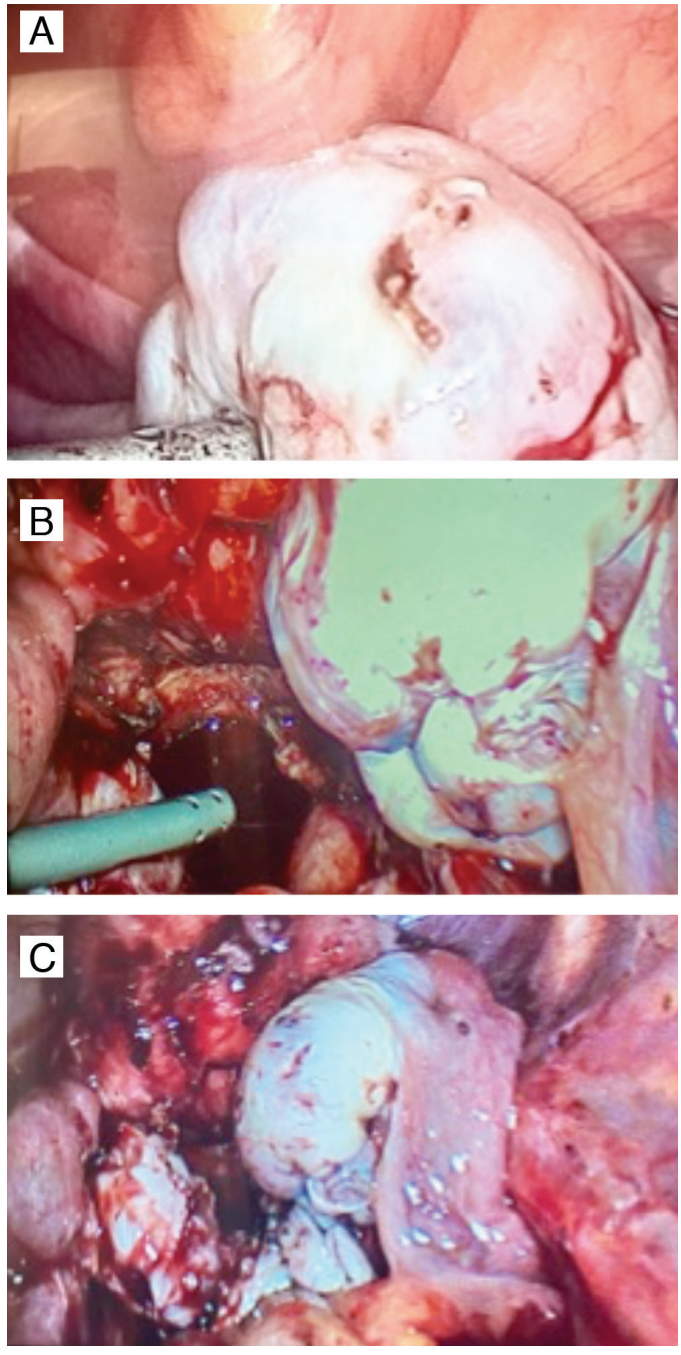

Figure 1. (A-C) Type 1 endometriomas from implanted endometrial-like tissue on the ovarian cortex

subsequent live birth rates was seen (50-76%) when compared to controls (7.4%). In this study, 93.8% of patients that tested positive for BCL-6 had laparoscopic findings of endometriosis (19). A retrospective study by Nezhat et al. (22) on reproductive age females going through IVF treatment with endometrial BCL-6 overexpression who underwent laparoscopic surgery for treatment of suspected endometriosis showed that three-quarters of patients (74.7%, n=56) had a histologically confirmed diagnosis, while 21.3% were diagnosed visually through the presence of ovarian endometriotic implants (n=16). Women with at least six months of postoperative follow-up were assessed for reproductive outcomes (n=40), resulting in a clinical pregnancy rate of 90.0%. The positive predictive value (PPV) of BCL-6 testing was found to be as high as 96% for the diagnosis of endometriosis, similar to previously reported rates (19,22).

Conclusion

According to ASRM, approximately 50% of patients with unexplained infertility may have undiagnosed endometriosis (8). Although women diagnosed with unexplained infertility and recurrent pregnancy loss undergo IVF treatments, they seldom seek surgical diagnosis of endometriosis, even though persistent endometriosis could affect the success rate of IVF. Testing for endometrial BCL-6 may help determine high-risk endometriosis patients with other inflammatory pathologies who could be good surgical candidates. Endometrial BCL-6 testing has a high PPV that could help physicians and patients undergoing infertility treatment to seek surgical evaluation for endometriosis, to improve their reproductive outcomes (22).

Peer-review: Externally and internally peer-reviewed.

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

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

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Efficacy trials comparing dosages of vitamin D and calcium co-supplementation in gestational diabetes mellitus patients require a methodological revamp

To the Editor,

In this letter, I want to discuss a recently (2021) published clinical trial report by Gunasegaran et al. (1) in the Journal of Obstetrics and Gynaecology Research on the efficacy of prenatal vitamin D and calcium co-supplementation in gestational diabetes mellitus (GDM) patients. The report suggests that co-supplementation with vitamin D 1,000 IU and calcium 1,000 mg is relatively beneficial compared to co-supplementation with vitamin D 250 IU and calcium 500 mg in achieving blood glucose and lipid homeostasis in GDM patients on medical nutrition therapy (1). The co-supplements were given daily for six weeks (1).

The study is important as antenatal glycemic control yields better perinatal outcomes in GDM patients and their neonates. Hyperglycemia in GDM occurs in late pregnancy, due to inadequate insulin secretion and consequent failure to counteract the physiological insulin resistance. Furthermore, homeostasis of the blood lipid profile in GDM patients is also critical as its derangement is related to diabetes and cardiovascular risk in the long term. Several nutritional supplements have been tested to see their effect on these markers, including vitamin D, probiotics, omega-3 fatty acids, and so on. Vitamin D is crucial among these, as an association between its deficiency and GDM has been reported in observational studies. However, the physiologic role of vitamin D in pregnancy remains poorly understood. Since regular supplementation of vitamin D and calcium in pregnancy is not yet established, it's a hot topic in obstetric medicine, making the trial by Gunasegaran et al. (1) relevant in this milieu. It is perhaps the first trial from the Indian subcontinent in this context and important addition to the existing literature, predominantly sourced from Iran (2,3). The absence of participant attrition from the trial added merit to it (1). Regarding its limitations, the authors have highlighted its lack of blinding of study participants and personnel and heterogeneity across the participants' baseline vitamin D status (1).

Given the importance of the trial, its scientific appraisal is critical, and I have two viewpoints to share in this regard. First, regarding the statistically significant outcomes, the risk of type 1 error plausibly remains high due to the relatively small sample size of the trial (70 participants data analyzed) (1,4). Second, although the trial (1) depicted statistically how changes in different outcomes post-intervention varied between the compared intervention groups, the inclusion of a placebo arm would have reasonably enhanced its methodological rigor (5). A placebo arm-based juxtaposition is critical before ascertaining comparative efficacy between high and low doses of vitamin D and calcium co-supplementation to investigate if these respective interventions are better than placebo.

To conclude, since every piece of evidence sourced from different clinical trials contributes to the obstetric medicine evidence pool, future trialists may consider the strengths and limitations of this trial while preparing their trial protocol. Therefore, double-blinded, adequately powered trials of factorial design may be the methodological foundation to disentangle the metabolic effects of prenatal vitamin D, calcium, their co-supplemented form, and their different dosages in GDM patients.

Received: 29 September, 2021 **Accepted:** 09 March 2022

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Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2022.2021-9-23

Acknowledgement: *I thank Mr. Chris Nowlan for providing relevant literature to read.*

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A survey study on the attitudes of pregnant women to COVID-19 vaccine in Turkey

To the Editor,

It is evident that pregnant women and babies have suffered damage throughout the Coronavirus disease-2019 (COVID-19) pandemic (1). Hence, immunization is critically important for pregnant women. The American College of Obstetricians and Gynecologists recommends that all eligible individuals over the age of 12 years, including pregnant and breastfeeding women, receive a COVID-19 vaccine or series of vaccines (2). Although evidence on the safety of COVID-19 vaccinations in pregnancy is limited, high-quality findings demonstrate its reliability, and further evidence emerges day by day (3). Nevertheless, despite all available knowledge and the positive findings of the research, the concerns and rejection of COVID-19 vaccination by pregnant women is a critical issue that should be addressed.

We conducted a survey to assess whether pregnant women would trust the vaccine or not, even though human and/or animal experiments proved the safety and efficiency. The survey was conducted face-to-face with pregnant women who were admitted to our obstetrics outpatient clinic between February and April 2021. Five hundred and eight pregnant women agreed to participate in the survey.

We found that 50.8% of pregnant women do not want to be vaccinated during pregnancy. Even if animal experiments have proven the safety of the vaccine, 90% of these unwilling women still do not want to be vaccinated. Only 3.8% of these women changed their opinions positively. However, if the reliability of the vaccine was proven in human subject research, 24.8% of them would reconsider their refusal to be vaccinated. The biggest concern of women regarding the vaccination is that they are pregnant. If these women had not been pregnant, only 37% would have refused vaccination. The primary concerns of the participants were preterm birth (29.2%) and miscarriage (26.2%). The idea of harm to the fetus was a concern of only a small proportion of the women. When pregnant women begin breastfeeding, the rate of refusal to be vaccinated reduced to 20.3%. In addition, 45.3% of the participants believe vaccines will not be successful. If Turkey produced its own vaccine, the rate of participants who accept vaccination rises to 57.7%.

Inadequate data, health policies, and agendas create distrust in pregnant women against vaccines. The two most common concerns of pregnant women are premature birth and miscarriage. It is clear that additional studies, especially those conducted during the early pregnancy, including the preconception period and long-term follow-up, are significantly necessary. Producing a vaccine improves pregnant women's confidence in countries where nationalism is prominent owing to sociopolitical positions, such as in Turkey.

This current study was approved by the Institutional Review Board (no: E-12405952-050.05.04-115097) and was performed under the rules of the Declaration of Helsinki. The patients have given their informed consent for the manuscript to be published.

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Received: 26 August, 2021 **Accepted:** 25 January, 2022

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Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2022.2021-8-13

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Cardiophrenic and costophrenic lymph node resection via subxiphoid approach only

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Abstract

When enlarged cardiophrenic lymph nodes (CPLN) are resected the impact on survival is still uncertain, but resection contributes to accurate staging and complete gross resection in advanced ovarian cancer. CPLN resection can be performed via video-assisted thoracic surgery or transabdominally through the subxiphoid or transdiaphragmatic routes. The subxiphoid approach is used to reach the prepericardiac nodes located in the anterior mediastinum. The transdiaphragmatic route is used to remove the costophrenic and supradiaphragmatic paracaval lymph nodes located in the middle and posterior mediastinum, respectively. However, the transdiaphragmatic approach necessitates diaphragm opening and, in most cases, liver mobilization. Costophrenic nodes can be resected through the subxiphoid route in appropriate patients without opening the diaphragm. Thus, the subxiphoid approach may be preferred to remove the costophrenic lymph nodes, in cases in whom diaphragm resection is not anticipated, and especially when the resection procedure is planned to include the prepericardiac nodes. In this video article, we present the method of resecting both prepericardiac and costophrenic lymph nodes using only the subxiphoid approach in a case of advanced ovarian cancer. The subxiphoid virtual space between the pericardium and diaphragm was developed. The observed and palpated CPLNs were dissected and excised from the prepericardiac and right latero-cardiac spaces. Thereafter, diaphragm peritoneum beneath the right costophrenic nodes was dissected. After identifying any enlarged costophrenic nodes by palpation, the sternal and costal diaphragmatic attachments were incised and the right latero-cardiac space was extended. When the single enlarged node was reached, it was grasped and pulled with curved-ring forceps and ultimately resected. (J Turk Ger Gynecol Assoc 2022; 23: 124-5)

Keywords: Cardiophrenic lymph node, costophrenic lymph node, subxiphoid approach, advanced ovarian cancer

Received: 7 December, 2021 **Accepted:** 25 January, 2022

Introduction

The main goal of surgery in advanced ovarian cancer is finalizing the operation with no gross residual disease. Even though the impact of resection of enlarged cardiophrenic lymph nodes (CPLN) on survival is still a matter for debate, it contributes to accurate staging and complete gross resection in advanced ovarian cancer (1). CPLN resection can be performed via video-assisted thoracic surgery (VATS) or transabdominally, through the subxiphoid or transdiaphragmatic routes. While using VATS will usually need the involvement of a thoracic surgeon, the subxiphoid and transdiaphragmatic approaches can be successfully performed by gynecological oncologists in many centers (2). The subxiphoid approach is normally used to reach the prepericardiac nodes, located in the anterior mediastinum. The transdiaphragmatic route is used to remove the costophrenic and supradiaphragmatic paracaval lymph nodes, located in the middle and posterior mediastinum, respectively (3). However, the transdiaphragmatic approach necessitates diaphragm opening and, in most cases, liver mobilization. Costophrenic nodes can be resected through the subxiphoid route in appropriate patients without opening the

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Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2022.2021-9-2

diaphragm (4). Thus, the subxiphoid approach may be preferred to remove the costophrenic lymph nodes, in cases in whom diaphragm resection is not anticipated, and especially when the resection procedure is planned to include the prepericardiac nodes. In this video article, we present the method of resecting both prepericardiac and costophrenic lymph nodes through the subxiphoid approach during interval cytoreduction surgery in a case of advanced ovarian cancer. The patient was 79-years old. After receiving three cycles of platinum-based chemotherapy, she was well enough for surgery. However, tomography demonstrated persisting enlarged CPLNs (Figure 1). Therefore, CPLN resection was planned during the interval cytoreduction. The subxiphoid virtual space between the pericardium and diaphragm was developed. The observed and palpated CPLNs were dissected and excised with their fatty pads from the prepericardiac and right latero-cardiac spaces (Figure 2). Thereafter, the automatic retractor blade was moved laterally, and diaphragm peritoneum beneath the right costophrenic nodes was dissected to achieve better exposure. After investigating any enlarged costophrenic nodes by palpation, which identified a single enlarged node, the sternal and costal diaphragmatic attachments were incised and the right latero-cardiac space was extended. When the node was reached, it was grasped and pulled with curved-ring forceps and resected using an ultrasonic device (Figure 3). Finally, the incision was closed with non-absorbable, interrupted sutures (Video 1). Pathological evaluation of seven lymph nodes identified two that were metastatic.

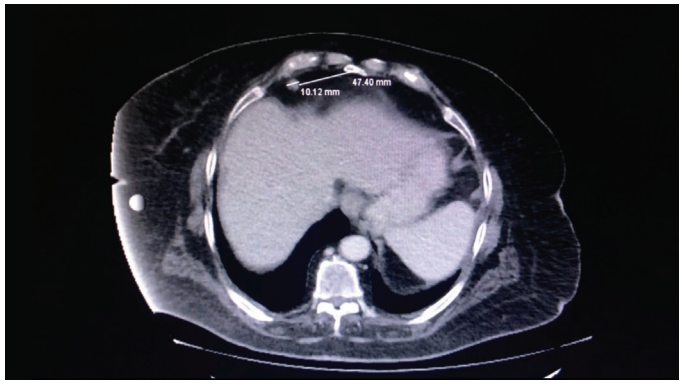

Figure 1. Enlarged right costophrenic lymph node approximately 5 cm from the xiphoid and sternum on computed tomography

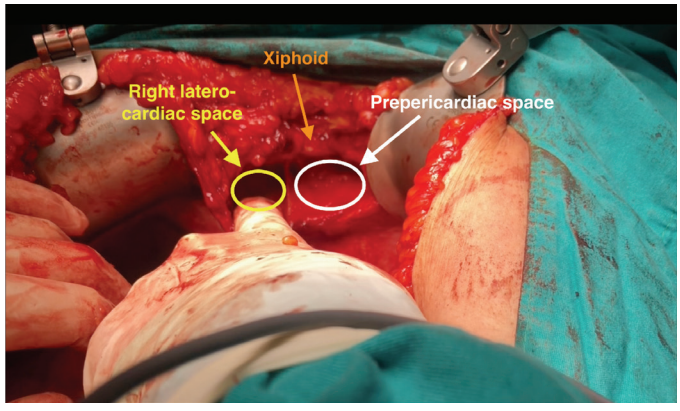

Figure 2. Prepericardiac and right latero-cardiac spaces

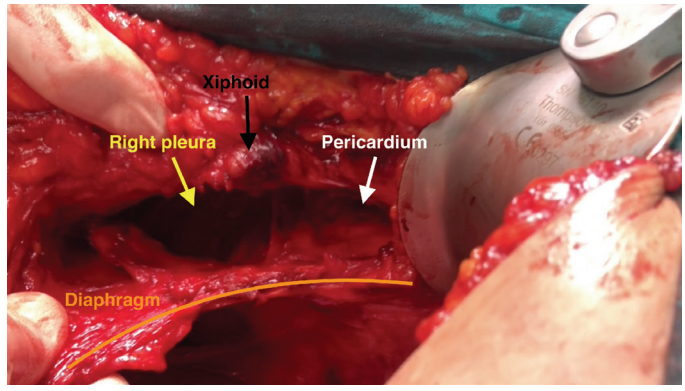

Figure 3. View of the operation field after completing lymph node dissection

Video 1. Cardiophrenic and costophrenic lymph node resection via subxiphoid approach only

https://www.doi.org/10.4274/jtgga.galenos.2022.2021.9-2.video1

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

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

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Ovarian suspension loop: an assembled device for ovarian lifting and immobilization during laparoscopic cystectomy

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Abstract

The mobility and smooth surface of the ovaries can pose a challenge during laparoscopic cystectomy, with difficulties in manipulation and visualization. We describe assembling a device for ovarian lifting and immobilization that utilizes a nylon suture and a "scalp vein set" to create a loop. The loop can be passed into the pelvic cavity and then slid beneath the ovary, elevating and stabilizing it during surgery without the need to puncture the ovarian tissue or grabbing and damage the utero-ovarian infundibulopelvic ligaments. This device is inexpensive, and its components are easily accessible. This assembled device prevents repetitive falling of the ovary into the pelvic cavity, facilitates laparoscopic ovarian cystectomy, and saves operative time. (J Turk Ger Gynecol Assoc 2022; 23: 126-9)

Keywords: Ovary, adnexal cyst, ovarian cystectomy, adnexal mass, suspension loop, ovarian lifting

Received: 04 December, 2021 **Accepted:** 20 March, 2022

Introduction

It is widely recognized that laparoscopic surgery for gynecologic disorders confers many benefits (1), but sometimes there are difficulties in manipulating the ovaries during minimally invasive surgery (2), especially in robotic surgery (1). Problems arise from the fact that ovaries can be very mobile due to their slightly flexible attachments to the utero-ovarian and infundibulopelvic ligaments. Also, the convex and smooth surface of the ovary often makes them slippery, preventing them from being grasped easily with laparoscopic instruments. Meanwhile, gripping the utero-ovarian and infundibulopelvic ligaments with a grasper can cause damage to these relatively delicate structures. Therefore, laparoscopic handling of the ovaries can represent a challenge for many gynecologists. At times it can take an excessive amount of time during a laparoscopic cystectomy to keep the ovary relatively immobilized in order to open the cortex (2,3).

One approach utilized by some surgeons is to place a laparoscopic device, such as a grasper, under the ovary, in order to raise it and prevent it from falling back to the pelvic floor.

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Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2022.2021-10-12

Some surgeons grasp the utero-ovarian or infundibulopelvic ligament to lift or immobilize the ovary. However, if this is not done cautiously, the grasper can damage these structures. Furthermore, using an instrument in this manner occupies one of the ports (2,3). Ovarian suspension with adjustable sutures with penetration of the cyst or ovarian parenchyma is another solution that has been used (4,5).

Material and Methods

This study aims to describe assembling a device for ovarian lifting and immobilization that utilizes a nylon suture and a "scalp vein set" to create a loop that can be passed into the pelvic cavity. The only required equipment for assembling a loop is a nylon suture 0 or 1, and a "scalp vein set"; any size can be used. The scalp vein catheter tube diameter is smaller than the intravenous line tube and it is easier to pass through the port (Figure 1a). Dependent on the thickness of the abdominal wall, a length of about 25-35 centimeters (cm) of the nylon thread is cut. Also, depending on the length of the mesovarium, about 8-12 cm of the catheter tube of the scalp vein set is cut (Figure 1b). The nylon thread then passed through the catheter tube, and the two ends are tied to make a loop. The knot can be pushed into the catheter tube to be hidden (Figure 1c). The assembled device is now sent into the pelvic cavity through one of the laparoscopic ports (Figure 2a). The abdominopelvic wall is checked for a suitable location to insert a fascial closure device for suspending the ovary. The nylon-string end is then grasped and withdrawn by the fascial closure device and secured to the skin surface by a Kelly clamp (Figure 2b-d). The two ends of the catheter tube are held by two grasping forceps to slide the loop beneath the ovary and

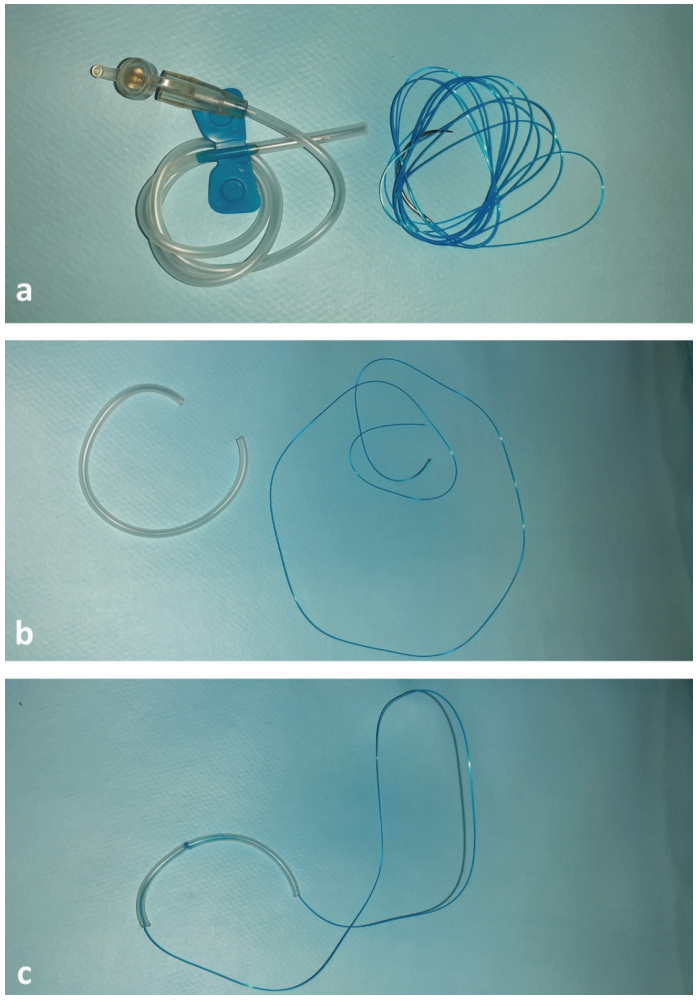

Figure 1. (a) The required materials for preparing the loop, including a nylon suture and a scalp angiocath (scalp vein catheter), (b) Nylon thread and the catheter tube are cut and separated as needed depending on the pelvic dimensions, size of the cyst, length of the mesovarium and the thickness of the abdominal wall and (c) the nylon thread passed through the catheter tube, and its two ends are tied. By holding the catheter tube and pulling the thread, the knot can be directed into the catheter tube to be hidden

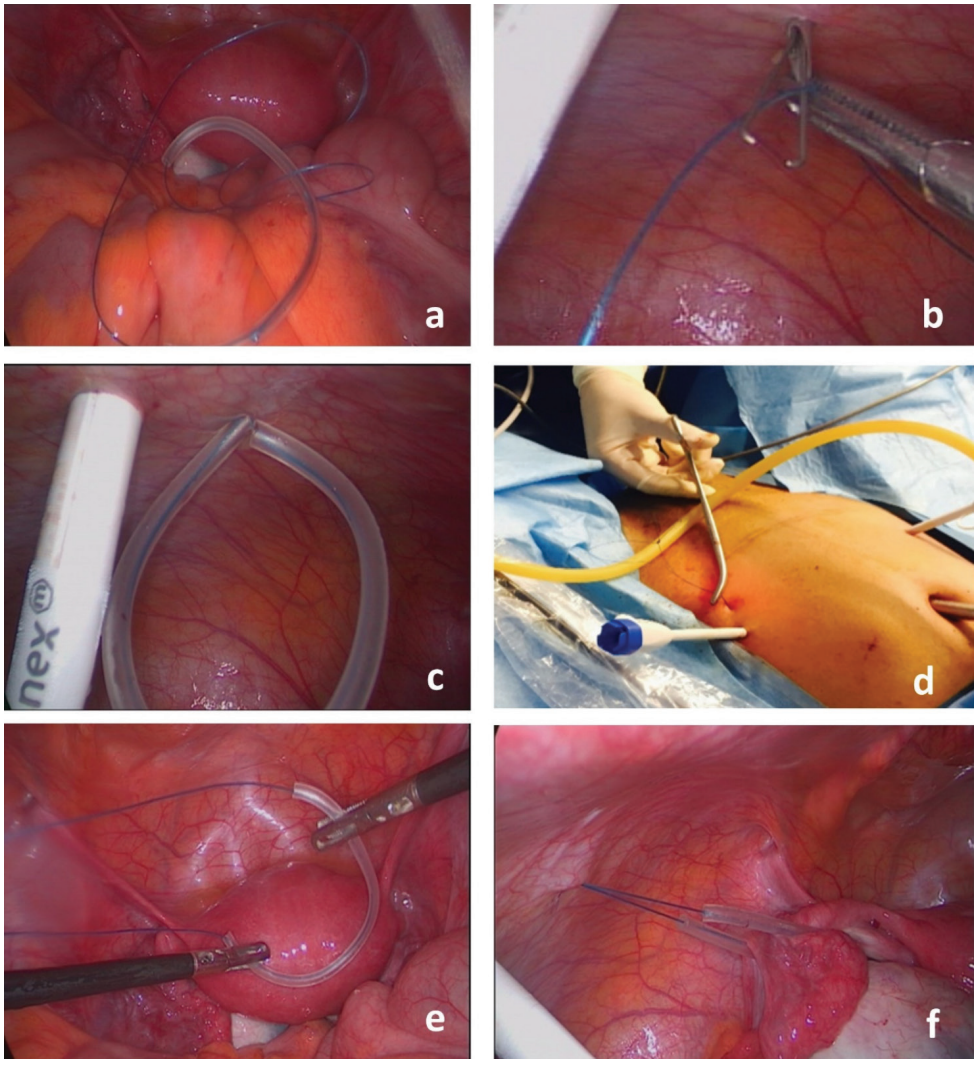

Figure 2. (a) The loop entered through the umbilical port; (b-d) the best site on the abdomen in line with the suspension location identified through appropriate mapping where the facial closure device inserted to retrieve the nylon thread and hold it with a clamp, and (e, f) the catheter tube, with its two ends held by two graspers is directed beneath the adnexa. Tension is applied from outside to provide a relatively fixed position for the adnexa

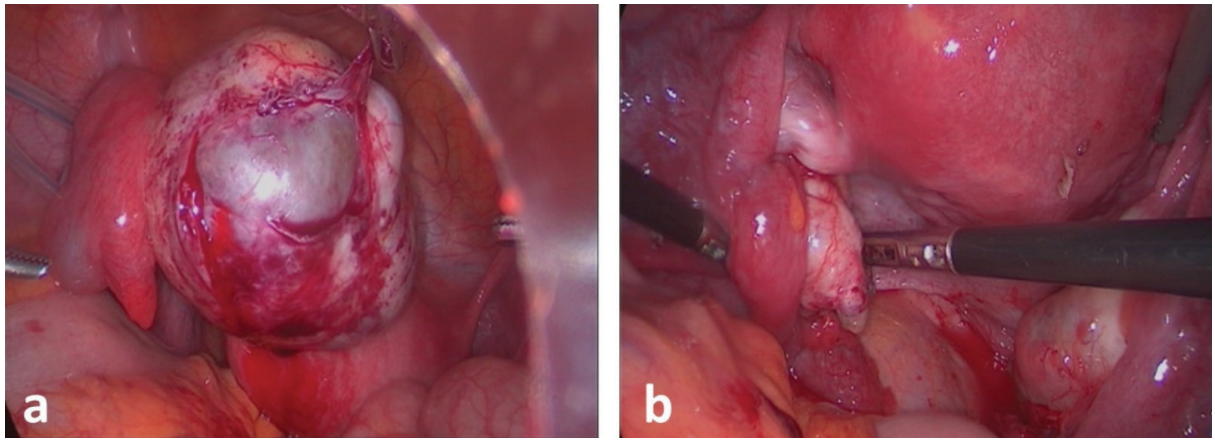

Figure 3. (a) During cystectomy when the ovary has a stable orientation and (b) after cystectomy when the adnexa is in an appropriate position

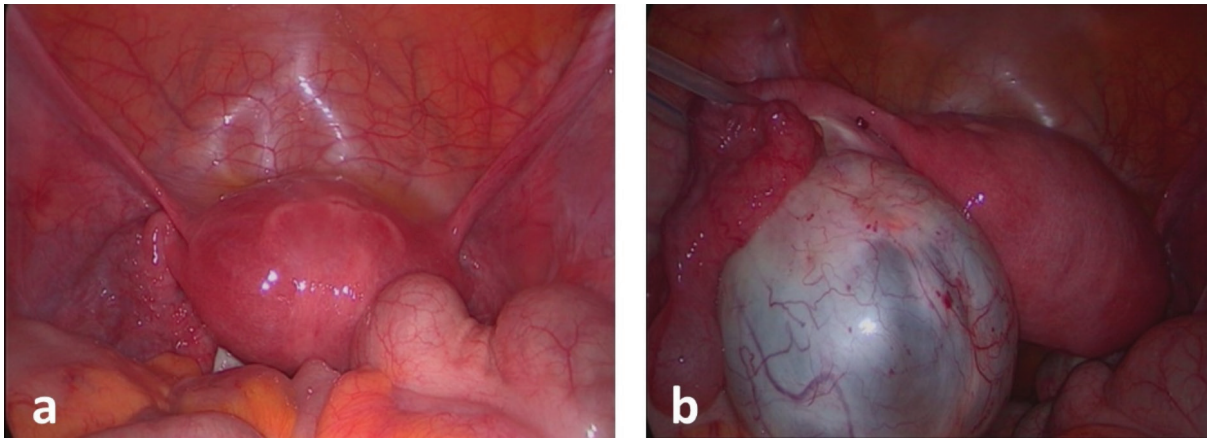

Figure 4. (a) Position of ovary and cyst (before), and (b) after suspension by loop

elevate it (Figure 2e, f). The tension on the string, and therefore the ovary, can be adjusted as needed. It is, of course, essential to avoid excessive traction of the adnexa so as not to interfere with the ovary's blood supply. Later, the ovary is released after surgery accomplishment, and then one of two strands of the nylon thread is cut above the skin, and the other one pulls out. Then, the catheter tip is grasped and taken out from the port (Figure 3a, b). The video shows how the surgeon lifts and immobilizes the ovary during cystectomy surgery using an assembling device (Video 1).

Video file: Thirty one year-old female, gravida 1, para 1 with previous history of cesarean section who was referred with the complaint of left lower pelvic pain for two months. Sonography revealed a 5-6 cm dermoid cyst in the left ovary. During laparoscopic cystectomy, the ovarian suspension loop effectively prevented repetitive falling of the ovary into the pelvic cavity and provided relative stability of the ovary during manipulation.

Conclusion

The ovarian suspension loop effectively prevents repetitive falling of the ovary into the pelvic cavity. It provides relative stability of the ovary during manipulation without any penetration of the cyst or ovarian parenchyma (Figure 4a, b). This device is inexpensive, and its components are easily accessible. By using this assembled device, laparoscopic ovarian cystectomy facilitates and saves operative time.

Video 1. This shows how the surgeon lifts and immobilizes the ovary during cystectomy surgery using an assembling device

https://www.doi.org/10.4274/jtgga.galenos.2022.2021.10-12.video1

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

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

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CONGRESS CALENDER

INTERNATIONAL MEETINGS

(for detailed International Meeting please go website:
http://www.medical.theconferencewebsite.com/conferences/obstetrics-and-gynaecology)

May 28-June 01, 2022	**XIV. TURKISH GERMAN GYNECOLOGIC CONGRESS, Antalya, Turkey**
June 29-July 02, 2022	XXVIII European Congress of Perinatal Medicine (ECPM), Lisbon, Portugal
July 03-06, 2022	European Society of Human Reproduction and Embryology (ESHRE) 38th Annual Meeting, Milan, Italy
September 16-18, 2022	32nd World Congress on Ultrasound in Obstetrics and Gynecology, Venue not announced yet
September 30-October 02, 2022	International Gynecologic Cancer Society (IGCS) 2022, Meeting, New York, NY, United States
October 02-05, 2022	ESGE 31st Annual Congress, Lisbon, Portugal
October 22-26, 2020	American Society for Reproductive Medicine (ASRM) 78th Annual Meeting, Anaheim, CA, United States
October 26-29, 2022	18th World Congress on Menopause, Lisbon, Portugal
November 24-26, 2022	The 30th World Congress on Controversies in Obstetrics Gynecology & Infertility (COGI), Amsterdam, The Netherlands
November 30-December 04, 2022	The 51st American Association of Gynecologic Laparoscopists (AAGL) Global Congress on Minimally Invasive Gynecologic Surgery (MIGS), Denver, CO, United States

CONGRESS CALENDER

NATIONAL MEETINGS

(for detailed International Meeting please go website:
http://www.kongre2022.com)

May 28-June 01, 2022	**TAJEV - 14. TÜRK- ALMAN JİNEKOLOJİ KONGRESİ, Antalya, Türkiye**
September 08-11, 2022	3. Uluslararası KKTC Obstetri ve Jinekoloji Kongresi, Girne, KKTC
September 22-25, 2022	4. Obstetrik ve Jinekoloji Tartışmalı Konular Kongresi, Antalya, Türkiye
September 23-25, 2022	Pelvik Taban ve Kozmetik Jinekoloji Kongresi, İstanbul, Türkiye
September 30-October 02, 2022	10. Ulusal Ürojinekoloji Kongresi, İstanbul, Türkiye
October 12-16, 2022	Türkiye Maternal Fetal Tıp ve Perinatoloji Derneği 13. Ulusal Kongresi, Antalya, Türkiye
November 02-06, 2022	IX. Üreme Tıbbı ve Cerrahisi Derneği Kongresi, Antalya, Türkiye
November 03-06, 2022	Uluslararası Jinekoloji ve Obstetri Kongresi, Muğla, Türkiye
November 10-13, 2022	10. Üreme Sağlığı ve İnfertilite Kongresi, TSRM 2022, Girne KKTC