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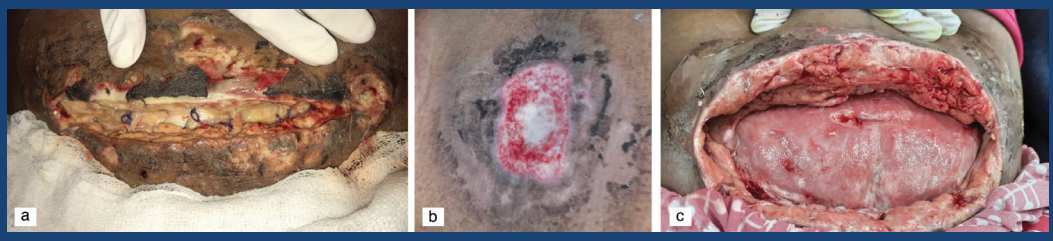

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2024

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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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All manuscripts should be accompanied by an abstract. A structured abstract is required with original articles and it should include the following subheadings: Objective, Material and Methods, Results and Conclusion. A structured abstract is not required with review articles. The abstract should be limited to 250 words for original articles and review articles.

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Describe the plan, the patients, experimental animals, material and controls, the methods and procedures utilized, and the statistical method(s) employed. In addition to the normal peer review procedure, all randomized controlled trials (RCTs) submitted to the journal are sent to members of a team of professional medical statisticians for reviewing.

Address "Institutional Review Board" issues as stated above. State the generic names of the drugs with the name and country of the manufactures. Provide information on informed consent and ethics committee approval.

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

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Number references in Arabic numerals consecutively in the order in which they are mentioned in the text starting with number "1". Use the form of the "Uniform Requirements for Manuscript Submitted to Biomedical Journals" (http://www.amaassn.org/public/peer/wame/uniform.htm). If number of authors exceeds seven, list first 6 authors followed by et al.

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Book;

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Editorial

Dear Colleagues,

It is my great pleasure to introduce the first issue of the "Journal of the Turkish-German Gynecological Association (J Turk Ger Gynecol Assoc)" in the publishing year of 2024. This issue is consisted of seven articles, and one review that we hope you will read with interest. Also you may have the opportunity to read the quiz. Here we share some of our favorite articles that were published in this issue of the journal.

Up to 30% of women experience abnormal uterine bleeding (AUB), a common gynecological issue. For women who are able to handle it, office hysteroscopy offers many benefits. By detecting and treating AUB accurately and safely, it spares them from the possible risks associated with general anesthesia and hospital admission. You will have the opportunity to read an article investigating the benefits and viability of "see-and-treat" hysteroscopy using a morcellator without anesthesia in patients with AUB.

The annual reports on assisted reproductive technology (ART) aid in the provision of reliable and aggregated data to support healthcare policy, allow for the computation of related expenses, ease the development and accessibility of treatment, and improve the standard of care rendered. You will read a multicenter descriptive survey, describing the clinical outcomes of ART cycles in Turkey in 2019 as well as the distribution of demographic characteristics through aggregated, anonymized data.

You will also have the opportunity to read a review investigating abnormal coiling of the cord and associations of abnormal coiling with various pregnancy factors

I would also like to invite you to join us for our "Symposium on Current Approaches in Obstetrics and Gynecology", which will be held in İstanbul on May 31-June 1 2024. The scientific programme of the symposium includes many distinguished scientists and researchers both from Turkey and Europe.

Dear Esteemed Readers, Authors and Reviewers,

We received more than 159 article submissions in 2023, we have already published more than 51 articles, although some of our articles are still under evaluation. Our published articles cover a wide range of obstetrics and gynecological topics. This is our chance to express our gratitude to everyone who sent in entries for our journal in the previous year. We are appreciative to our authors, reviewers, and readers.

Please visit us online at www.jtgga.org and keep in touch with us by following us on Twitter @JtggaOfficial.

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

The role of hysteroscopy with morcellator without anesthesia in the management of abnormal uterine bleeding

Francesco Giuseppe Martire[1,2], Luca Labanca[2], Matteo Giorgi[3], Aikaterini Selntigia[1], Consuelo Russo[1], Gabriele Centini[3], Alessandro Ginetti[3], Claudia D'Abate[3], Stella Capriglione[2], Caterina Exacoustos[1], Francesco Catania[2], Errico Zupi[3], Lucia Lazzeri[3]

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[3]Department of Molecular and Developmental Medicine, Division of Obstetrics and Gynecology, University of Siena, Siena, Italy

Abstract

Objective: To evaluate the feasibility of hysteroscopy with morcellator without anesthesia and the diagnostic accuracy of 2D, 3D and power Doppler transvaginal sonography (TVS) in patients with abnormal uterine bleeding (AUB).

Material and Methods: This was a retrospective study including women with AUB. All patients underwent 2D, 3D and power Doppler TVS evaluation of the uterine cavity, and patients with suspicion on ultrasound (US) of endometrial pathology (EP) underwent hysteroscopy with morcellator without anesthesia. The painful symptomatology was assessed during the procedure using a visual analogue scale (VAS). Additionally, histological evaluation was performed.

Results: A total of 182 women underwent US imaging, of whom 131 (72%) had hysteroscopy. 130/131 patients completed the hysteroscopic examination with good compliance (VAS <4). One patient (0.8%) was unable to complete the procedure due to nulliparity and cervical stenosis. Of the 130 patients the US diagnosis was confirmed in 120 (92.3%), while in 10 patients (7.7%) the hysteroscopic diagnosis was different from the US diagnosis. Histological examination confirmed benign endometrial polyps in 115/130 patients (88.5%), while premalignant conditions were diagnosed in 3/130 patients (2.3%) and malignant conditions in 2/130 (1.5%). Of the 10 patients with endometrial thickening, two were diagnosed with a malignant condition.

Conclusion: This study confirmed the feasibility of managing patients with AUB and suspicion of EP using "see-and-treat" hysteroscopy with morcellator without anesthesia. This procedure has the potential to yield desired outcomes while minimizing pain and discomfort, presenting a feasible outpatient approach for both treating and preventing endometrial carcinoma without requiring anesthesia. (J Turk Ger Gynecol Assoc 2024; 25: 1-6)

Keywords: Abnormal uterine bleeding, endometrial polyp, hysteroscopy, morcellator

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Introduction

Abnormal uterine bleeding (AUB) is a widespread gynecological problem, affecting up to 30% of women (1). Endometrial polyps are one of the most common causes of uncontrolled uterine bleeding in both pre- and post-menopausal women (2). Transvaginal sonography (TVS) is the primary modality for locating endometrial polyps and identifying endometrial pathology (EP), in some cases using contrast saline infusion or gel installation, while the gold standard for diagnosis and treatment is hysteroscopy (3,4).

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Practice-based operative hysteroscopy is generally well tolerated by patients (5), thus avoiding many traumatic uterine procedures and allowing a more direct strategy for the assessment and treatment of a numerous intrauterine pathologies, at the same time that the diagnosis is made (6). Hysteroscopy may be suitable in women with AUB if there are ultrasound (US) signs of EP (7), given the excellent diagnostic accuracy in the detection of uterine pathologies.

Endometrial polyps may be treated by uterine curettage and grasping forceps, but this procedure is time-consuming, and may not yield satisfying results. Usually, small polyps may be removed by hysteroscopic grasping instruments or by electrosurgical resection. However, these strategies are challenging when there are large or multiple polyps. In these cases, hysteroscopic morcellation is faster, less painful, and more effective, allowing a more complete excision of endometrial polyps than electrosurgical resection (9,10).

Outpatient hysteroscopy provides significant advantages to women who can tolerate it, as they can get safe and precise detection and treatment of AUB, avoiding the potential complications of general anesthesia and hospital admission (11). For clinical management in the outpatient setting, the main objectives are to manage pain, improve efficiency, and reduce the duration of procedures while maintaining adequate accessibility standards for both diagnostic and therapeutic outpatient hysteroscopy.

This retrospective study evaluated the feasibility of "see-and-treat" hysteroscopy with morcellator without anesthesia in patients with AUB, and investigated the advantages that this procedure may offer regarding alleviation of pain, levels of patient discomfort, and improving clinical efficiency without sacrificing treatment and prevention of endometrial carcinoma.

Material and Methods

This retrospective, observational study included women with AUB referred to our hospital between November 2021 and December 2022, including patients with suspicion of EP such as polyps and endometrial thickening, and excluding patients with suspected intracavitary myomas. AUB was defined in childbearing age, as bleeding from the corpus of the uterus which was not controlled in duration, amount, frequency and/or regularity, while postmenopausal bleeding was defined as either any bleeding after menopause in women not on hormonal therapy or unexpected or heavy bleeding in women on hormonal therapy. Subjects were divided into premenopausal and menopausal groups. All patients underwent two-dimensional (2D), 3D and power Doppler TVS assessment of the uterine cavity. Subsequently, patients with suspicion of EP on TVS underwent hysteroscopy with morcellator without anesthesia, and were included in the study. All patients were subjectively evaluated for painful symptomatology during the procedure by means of completion of a visual analogue scale (VAS). Hysteroscopic diagnosis was also made and histological evaluation was performed in cases where samples were taken. Additionally, the accuracy of the TVS diagnosis was compared with respect to the hysteroscopic diagnosis.

The criteria for inclusion in this study were: women with AUB and TVS suspicion of EP; who underwent hysteroscopy with morcellator without anesthesia; and there was access to complete medical history, including symptoms and surgical reports. Exclusion criteria were; no suspicion of EP on TVS; being pregnant; and unavailable accurate medical history.

Clinical examination

The complete medical, surgical, and obstetrical history of the patients including age, body mass index [(BMI), in kg/m^2], age at menarche, gravidity, parity, and the mode of delivery were recorded. Demographic data, menstrual information, indication for hysteroscopy and imaging findings were collected.

Ultrasound examination

All TVS assessments and interpretations were performed by an experienced sonographer using a 4-9-MHz probe with a 3D facility (Voluson E6 or E10, GE Medical Systems, Zipf, Austria). Routinely, 2D US with greyscale and power Doppler for examination of the pelvis was carried out.

The uterus, myometrium, and endometrium were analyzed. The 2D examination was followed by the acquisition of the 3D volume of the uterus, with and without power Doppler, which is important to assess the uterine cavity morphology. TVS scans were performed using the International Endometrial Tumor Analysis (IETA) examination technique, and the US findings were described in IETA terminology (12).

Endometrial depth was measured in the sagittal plane including both endometrial layers. When intracavitary fluid was found, the two layers were measured separately, and the sum was recorded. Endometrial echogenicity was reported as uniform or non-uniform. The color-Doppler score is a subjective evaluation of the amount of color, reflecting the vascularity, and is scored as 1 (no color), 2 (minimal color), 3 (moderate color) or 4 (abundant color).

All data was recorded as 2D still images, 2D video-clips, and 3D volumes.

Hysteroscopy

All patients underwent hysteroscopy with morcellator using an Integrated Bigatti Shaver (Karl Storz, Tuttlingen, Germany) without anesthesia using normal saline (NaCl: 0.9%) as distention medium in an outpatient setting. The procedural time measurement began upon insertion of the instrument

using vaginoscopic access and continued until its removal. Painful symptoms were assessed during the procedure using a VAS, taking the mean score reported throughout the procedure. The hysteroscopic diagnoses of intracavitary pathologies were recorded for all patients. Removal of intrauterine pathologies with histological examination was performed for all patients.

Ethical approval

All involved patients gave their informed consent before the TVS examination and the hysteroscopy to permit the use of their data. The study was submitted and approved by the board of the USL Toscana Sud Est (approval number: 0002959, date: 22.11.2022).

Statistical analysis

Statistical analyses were performed using the SPSS v.15.0 (SPSS, Inc., Chicago, IL, USA). Continuous variables are reported as mean ± standard deviation (SD). Categorical variables are reported as a frequency or percentage. The statistical analyses initially assessed patient characteristics. Then the characteristics of hysteroscopy procedure and US, hysteroscopic and histological findings were evaluated in terms of percentage. Intergroup comparisons were performed using chi-square tests for categorical variables and independent sample t-tests for continuous data. Fisher's exact test was used to compare prevalence. Results with $p<0.05$ were considered statistically significant.

Results

A total of 182 women underwent TVS and 131 (72%) patients who matched the inclusion criteria were included. The characteristics of the study cohort are shown in the Table 1. The mean ± SD age of the patients was 49.7±5.2 years. Most patients (78.7%) had one or more pregnancies and 27.2% of patients were affected by hypertension, diabetes, and/or dyslipidemia. The majority (62.6%) were menopausal. None of the patients were undergoing hormone replacement therapy.

The cohort was divided into two subgroups: pre-menopausal patients (n=49) and menopausal (n=82) patients. There were no differences in between the two groups in terms of BMI, age at menarche, presence of metabolic diseases (hypertension, diabetes, and dyslipidemia), or indication for hysteroscopy (Table 1). Thus, the two groups were considered together for further analysis.

The characteristics of the hysteroscopic procedure used in the study are shown in Table 2. The hysteroscopic procedure was completed in 99.2%. One patient was unable to complete the procedure due to nulliparity and presence of cervical stenosis. The mean duration of the procedure was 7.3 minutes, while the mean VAS score reported was 2.5. The majority who completed the hysteroscopy (n=128, 98.5%) reported satisfaction with the procedure and setting. In two cases, complications involving fever and pelvic pain attributable to endometritis were reported 2 days after the procedure.

The results of the sonographic, hysteroscopic and histological evaluations are shown in Table 3. In 120 cases (92.3%), the diagnosis was consistent with both TVS and hysteroscopy, while in 10 patients (7.7%), hysteroscopy revealed the presence of an EP different from that suspected by the US. Histological examination confirmed benign endometrial polyps in 115/130 (88.5%), premalignant conditions (atypical endometrial hyperplasia) in 3/130 patients (2.3%) and malignant conditions (endometrial cancer) in 2/130 patients (1.5%). Among the 10 patients who received a diagnosis of endometrial thickening

Table 1. Patients characteristics in total study population, premenopausal group, and menopausal group

Patients characteristics	Total population, n (%)/ (mean ± SD)	Premenopausal group, n (%)/(mean ± SD)	Menopausal group, n (%)/(mean ± SD)
	131	49 (37.4)	82 (62.6)
Age (years)	49.7±5.2	43.5±4.6	51.1±4.2
BMI (kg/m^2)	27.8±2.1	25.6±2.5	28.3±1.7
Menarche (years)	12.0±1.8	11.8±1.6	12.2±2.0
Gravidity	2.3±0.8	2.2±1.2	2.1±1.1
Parity	1.5±0.6	1.6±0.7	1.8±0.4
Nulliparity	29 (22.1)	11 (22.4)	18 (21.9)
Hypertension	23 (17.5)	7 (14.3)	16 (19.5)
Diabetes	5 (3.8)	1 (2.0)	4 (4.9)
Dyslipidemia	9 (6.9)	3 (6.1)	6 (7.3)
Previous uterine surgery	16 (12.2)	5 (10.2)	11 (13.4)
On hormonal therapy	12.2% (16)	32.6% (16)	0.0% (0)

Data shown as n (%) or mean ± standard deviation, BMI: Body mass index

Table 2. The characteristics of hysteroscopic procedure, the evaluation of painful symptomatology and patients' satisfaction

Hysteroscopic procedure	Total population
Completed (n)/total (%)	130/131 (99.2%)
Not completed, (n)/total (%)	1/131 (0.8%)
VAS (mean ± SD)	2.5±0.8
Duration of procedure, minutes (mean ± SD)	6.5±1.6
Patient satisfaction, (n)/total (%)	128/131 (97.7%)
Complications, (n)/total (%)	2/131 (1.5 %)
SD: Standard deviation, VAS: Visual analogue scale	

Table 3. Sonographic, hysteroscopic and histological evaluation in total study population

Uterine pathology (n %; pts/)	Sonographic diagnosis	Hysteroscopic diagnosis	Histological diagnosis
Benign endometrial polyp, (n)/total (%)	125/131 (95.2%)	120/130 (92.3%)	115 (88.5%)
Endometrial thickening, n/total (%)	6/131 (4.6%)	10/130 (7.7%)	8 (6.1%)
Atypical endometrial hyperplasia, n/total (%)	0 (0.0%)	0 (0.0%)	3 (2.3%)
Endometrial cancer, n/total (%)	0 (0.0%)	0 (0.0%)	4 (3.1%)

during hysteroscopy, two patients were diagnosed with endometrial cancer, and eight patients were diagnosed with benign endometrial thickening.

Discussion

AUB is one of the most frequent gynecological complaints. Very often, AUB is the manifestation of a benign clinical condition, but sometimes it can be the first sign of malignant uterine pathology (13). Therefore, evaluation of the cause of AUB is important and should be performed promptly. Before obtaining the diagnosis and removing the organic EP causing AUB, the patient may be subjected to various procedures, such as diagnostic, and subsequently operative, hysteroscopy (14). The purpose of our study was to estimate the feasibility of hysteroscopy with morcellator without anesthesia and all outcomes regarding alleviating pain, discomfort, and improving efficiency without sacrificing treatment and prevention of endometrial carcinoma.

The hysteroscopic procedure was completed in 99.2% of the patients and 98% of patients who completed the hysteroscopy reported satisfaction with the procedure and setting, confirming that hysteroscopic morcellation was safe, effective and acceptable to patients, even in an outpatient setting (15). Pain might be a limitation for this procedure in an outpatient setting, but our results, in agreement with the literature, show that the technique is well tolerated patients (16).

Certainly, given the size of the instrument, hysteroscopy with morcellation can be more troublesome than a simple diagnostic hysteroscopy, however, unlike diagnostic hysteroscopy, which is often not curative in terms of treatment, this surgical method is both diagnostic and therapeutic. This technique is capable of removing and aspirating polyp tissue, reducing the time needed to reintroduce and to remove the hysteroscope to extract material through the cervix (17).

This is an important consideration because the possibility of diagnosing and treating the cause of AUB during a single procedure is likely to make patients more compliant, reducing the number of healthcare visits required to treat the condition. Therefore, the role of US evaluation is fundamental. It can guide towards diagnostic hysteroscopy, alleviating discomfort caused to the patient when there is suspicion of endometrial thickening or a malignant myometrial pathology (18,19) or towards a "see-and-treat" hysteroscopy with morcellator when endometrial polyps are identified. Diagnostic hysteroscopy remains an important tool for direct endometrial sampling and may be used as the first line treatment for the diagnosis of endometrial cancer and hyperplasia. In line with this, the results of the present study showed a high accuracy (92.3%) for TVS in the evaluation of the endometrial cavity.

Some authors have compared this surgical procedure with conventional operative hysteroscopy, with varying results. For some, hysteroscopic morcellation is more accurate, effective and safe because it does not involve electrical equipment. This eliminates the risk of electrical damage to the patient, such as tissue necrosis, uterine perforation or potential damage to other organs that may occur due to alterations in the current

circuit. In addition, hysteroscopic morcellation does not cause scars, the endometrium is better protected, and there are fewer postoperative complications (20-22). For others, this new technology is no better than traditional resection in terms of surgical success rate for treating endometrial lesions (23). Certainly, operative hysteroscopy can have advantages in certain types of intracavitary pathology, such as fibroids, especially those that are calcified or measuring >40 mm (24), or polyps located on the uterine fundus where it is more difficult to remove the entire lesion. In contrast, operative hysteroscopy may be more difficult in the presence of large or numerous polyps (25,26). This consideration once again highlights the importance of pre-operative US diagnosis in order to select the most appropriate therapeutic approach for each patient (12).

Another point of interest is the accuracy of the histological diagnosis, which may be improved with this method. In the present study, 3.1% of patients were diagnosed with endometrial malignancy. This may be attributed in part to the fact that one third of patients were affected by hypertension, diabetes, and dyslipidemia, all of which are contributing risk factors (27), and in part to the use of the technique that simultaneously excises and aspirates polyp tissue, not only reducing the formation of bubbles and the accumulation of excision tissue fragments, but also facilitating subsequent histological analysis (28). Within our cohort, no intraoperative complications were identified and only two postoperative complications were reported. This evidence supports the published reports on this technique, highlighting the role of hysteroscopic morcellation as a less complex surgery compared to conventional operative hysteroscopy (29).

However, hysteroscopic morcellation also has disadvantages, for example the inability to coagulate bleeding vessels encountered during surgery (20). In addition, the expense incurred for disposable devices (blades, tubings, etc.) needed to perform hysteroscopic morcellation is higher compared to the reusable instruments utilized for resectoscopy, but the possibility of performing a single procedure without the use of anesthesia and an operating room has been reported to more than compensate for the higher operating costs (30).

Conclusion

This study has provided additional evidence to support the opinion that “see-and-treat” hysteroscopy with morcellator without anesthesia is a safe and effective technique while having high patient acceptability. This procedure exhibits the potential to yield desired outcomes while minimizing pain and discomfort, presenting a feasible outpatient approach for both treating and preventing endometrial carcinoma. In deciding which technique should be used, a good pre-operative US evaluation plays a fundamental role. However, the tolerance for pain during practice-based operative hysteroscopy will vary greatly among women and will also depend on the skill level of the clinician performing the procedure, which may result in lower levels of patient acceptability.

Ethics Committee Approval: *All involved patients gave their informed consent before the TVS examination and the hysteroscopy to permit the use of their data. The study was submitted and approved by the board of the USL Toscana Sud Est (approval number: 0002959, date: 22.11.2022).*

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Evaluation of neonatal outcomes according to the specific absorption rate values of phones used during pregnancy

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Abstract

Objective: The aim was to compare neonatal outcomes according to cell phone specific absorption rate (SAR) levels and daily time spent on cell phones by pregnant women.

Material and Methods: Women who gave birth at Konya City Hospital between September 2020 and February 2021 were included in this retrospective study. Gestational ages, birth weight, birth length, head circumference, sex, 5-minute APGAR scores, neonate postpartum resuscitation requirement, delivery type, the model of phone used by the pregnant women, and the average time spent on the phone during a day were recorded. To determine the relation between the SAR values of the phones used and delivering a small for gestational age (SGA) baby, receiver operating characteristic curve analysis was performed.

Results: In total 1495 pregnant women were included. The rate of delivering a SGA fetus was significantly higher in women who used phones with higher SAR values ($p=0.001$). The cut-off value for the SAR level was 1.23 W/kg with 69.3% sensitivity and 73.0% specificity (area under the curve: 0.685; 95% confidence interval: 0.643-0.726). No correlation was found between time spent on the phone and SGA birth rate. Although both phone SAR values and time spent on the phone were higher in the symmetrical SGA group compared to the asymmetrical SGA group, the difference was not significant ($p>0.05$). Although the women who had preterm delivery had higher phone SAR values and had spent more time on the phone compared to those who had term deliveries, the difference was again not significant ($p>0.05$).

Conclusion: As the SAR values of cell phones used during pregnancy increased, there was a trend towards delivering a SGA baby. (J Turk Ger Gynecol Assoc 2024; 25: 7-12)

Keywords: Radiofrequency electromagnetic field, specific absorption rate, newborn, small for gestational age, pregnancy

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Introduction

With the development of the technology, cell phones have started to play an important role in our lives and are in widespread use (1). Cell phone use has increased during the last decades, with the number of cell phone users exceeding 4.5 billion and the number of smart phone users reaching 2.87 billion.

Cell phone technology is based on the transmission of voice, text, and images via radiofrequency electromagnetic fields (RF-EMFs). Due to the development of wireless local area networks, Bluetooth, and digitally enhanced wireless communications, the RF-EMF exposure rate is increasing (2). Since cell phones are used frequently, many scientific studies have been conducted investigating the effects of RF-EMFs on health and their relationship with health problems (3-5). The International Agency for Research on Cancer classified RF-EMFs as a possible carcinogen for humans in 2011 (6).

The rate of electromagnetic energy that is absorbed by body tissues is expressed as the specific absorption rate (SAR) (7).

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This value is related to the increase in temperature of body tissues. SAR is a measure showing the amount of energy absorbed, defined as Watts per kilogram of the body (8). It is closely related to the distance to the source. The magnitude of exposure decreases rapidly as the distance increases (9). It is also thought that exposure to this type of radiation may also cause adverse effects through free radical production without an increase in tissue temperature (10). In order to reduce these negative effects, the RF-EMFs associated with cell phone use have been reduced by the latest technological developments (such as 3G and 4G). However, there has been an increase in the duration of cell phone use (11).

There are studies that have concluded that cell phone calling and texting caused low abdominal and fetal exposure (12,13). In addition, an experimental study conducted in humans has shown that abdominal RF-EMF exposure can affect placental function (14). The studies concerning the effects of cell phone exposure during pregnancy and the effects on neonatal outcomes produced conflicting results regarding gestational age and low birth weight (15,16).

Different brands or even different models of the same brands of cell phones are known to have different SAR values (17). To the best of our knowledge, there is no published study that has investigated the effects of varying SAR levels of cell phones used during pregnancy on the pregnancy or neonatal outcomes.

In this retrospective study, the aim was to evaluate the demographic characteristics of the study population and neonatal outcomes in terms of specific cell phone SAR levels and daily time spent on cell phones during pregnancy. It was also planned to evaluate the effect of SAR levels and daily duration of cell phone use on giving birth to a small for gestational age (SGA) baby.

Material and Methods

Women who gave birth at Konya City Hospital between September 2020 and February 2021 were included in this retrospective study. The KTO Karatay University of Ethics Committee provided ethical approval for the present research (approval number: 2021/019, date: 09.02.2021). Written informed consent was obtained from all patients.

The gestational weeks of the women, the birth weight, birth height, head circumference, sex, neonate postpartum resuscitation requirement, 5-minute APGAR score, and health status data of the newborn babies, and the type of delivery were recorded. The phone numbers of the pregnant women included in the study were obtained from hospital records. The women who agreed to participate in the study were questioned about the presence of accompanying illnesses, the presence of problems during pregnancy follow-up, phone use during pregnancy, whether they used the same phone during pregnancy, the model of the phone they used, and the average daily phone use time, including texting, calling, and social media, during pregnancy.

SAR levels were recorded according to the brands and models of the phones (18).

Babies born below the 10^{th} percentile of birth weight standards for gestational age were defined as SGA, babies born between the 10^{th} and 90^{th} percentile were grouped as appropriate for gestational age, and those above the 90^{th} percentile were grouped as large for gestational age. The term "symmetrical SGA" refers to babies in whom all percentile values are below the 10^{th} percentile while asymmetrical SGA is used when the babies birth weight is below the 10^{th} percentile but there is a relative sparing of growth of the brain, cranium, and long bones (19).

Exclusion criteria

Infants born at any hospital except Konya City Hospital, infants of refugees, women with concomitant diseases during pregnancy (including diabetes mellitus, preeclampsia, and hypertension), women with multiple pregnancies, women who did not agree to participate in the study, infants with conditions affecting their birth weight, pregnant women whose data could not be accessed through the hospital data system, and women who used more than one phone with different SAR values during pregnancy were excluded from the study.

Statistical analysis

The statistical analyses were performed using IBM SPSS, version 22 (IBM Inc., Armonk, NY, USA). Data showing normal distribution were evaluated with an independent samples t-test, while variables without normal distribution were analyzed using the non-parametric Mann-Whitney U test. Categorical variables were analyzed using Fisher's exact and Pearson's chi-square tests. Results were expressed as mean ± standard deviation for normal distributions or median and 25^{th}-75^{th} percentile interquartile range. In addition, receiver operating characteristic (ROC) curve analysis was conducted to determine the cut-off value for the SAR level in babies who were SGA. P-values <0.05 were considered statistically significant.

Results

During the study period, 409 of 2286 pregnant women were excluded from the study as they were refugees. The data of the remaining 1877 pregnant women were accessed. In total 144 of these were excluded from the study as 125 had concomitant diseases and 19 of the pregnancies were multiple gestations (twins in 18, triplets in 1). In addition, 73 women declined to participate in the study. The phone numbers of 67 women could

not be obtained and 26 used two or more phones with different SAR levels. Furthermore, 17 were not using cell phones and 51 did not know the model of their cell phone. Four babies were excluded from the study due to additional conditions [Down syndrome (n=3) and achondroplasia (n=1)]. The remaining 1495 pregnant women and their babies were included in the study. The demographic and neonatal data of these 1495 pregnant women and their babies are given in Table 1.

Seven hundred and forty-four (49.8%) of the babies included in the study were male and 751 (50.2%) were female. The analyzed pregnancy was the median third (2-4) pregnancies of the women. Twenty of these babies (1.3%) needed resuscitation while 208 of them (13.9%) were SGA (Table 1). The babies were divided into two groups: SGA (n=208) and non-SGA (n=1287). The comparison of mothers in these two groups according to their time spent on the phone and the SAR levels of the phones they used during pregnancy is given in Table 2.

Time spent on the phone for the mothers of the SGA babies was similar to the time spent on the phone by mothers of non-SGA babies (p=0.969). In mothers who used higher SAR value phones, the rate of having an SGA baby was significantly higher (p=0.001) (Table 2). Since the incidences of exitus and stillbirths (16 babies) were low, no comparison could be made between these two groups.

When the maternal body mass index was compared between the SGA and non-SGA groups, no difference was found (p=0.706). There was no difference between the groups when the duration of exercise during pregnancy (absent, intermittent, regular), socioeconomic status (low, medium, high) and school graduation degree (illiterate, primary/secondary school, high school/university) were compared (respectively p=0.962; p=0.077; p=0.671). There was no difference between the groups in terms of smoking during pregnancy (p=0.054) (Table 2).

To determine the relation between the SAR values of the phones used and the probability of giving birth to an SGA baby, ROC curve analysis was performed. The cut-off value for the SAR level was 1.23 W/kg with 69.3% sensitivity and 73.0% specificity (area under the curve: 0.685; 95% confidence interval: 0.643-0.726) (Figure 1).

SGA babies were then further divided into two groups; symmetrical SGA (n=79; 38.0%) and asymmetrical SGA (129; 62.0%). The data on the SAR values of the phones used by mothers of asymmetrical and symmetrical SGA babies during

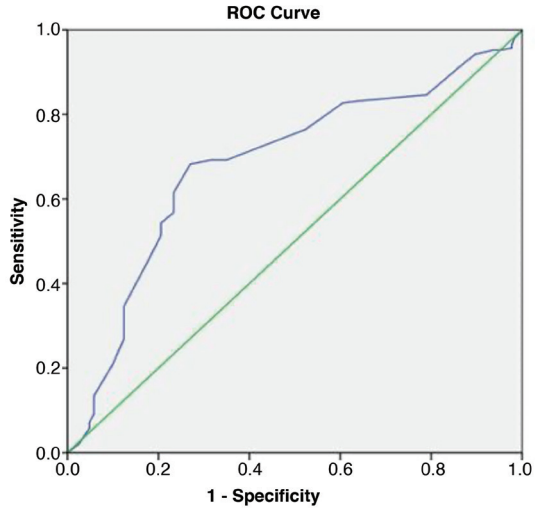

Figure 1. ROC curve analysis of the relationship between SAR value and SGA

ROC: Receiver operating characteristic, SGA: Small for gestational age, SAR: Specific absorption

Table 1. Demographic and neonatal characteristics of the pregnant women and their babies

Characteristics	n (%)
Gender (male/female)	744/751 (49.8/50.2)
Number of pregnancies (gravida)*	3 (2-4)
Gestational age (weeks)*	39 (38-40)
Birth weight (grams)*	3200 (2880-3500)
Birth length (cm)*	50 (49-52)
Birth head circumference (cm)*	35 (34-35)
Route of delivery (vaginal/cesarean section)	881/614 (58.9/41.1)
5-min Apgar*	10 (9-10)
Resuscitation need (+)	20 (1.3)
Alive/exitus/stillbirth	1479/6/10 (98.9/0.4/0.7)
SGA/AGA/LGA	208/1103/184 (13.9/73.8/12.3)
Phone SAR level (W/kg)*	1.09 (1.02-1.4)
Daily time spent on phone (minutes)*	190 (150-240)

*: Median (interquartile range: 25-75), SGA: Small for gestational age, AGA: Appropriate for gestational age, LGA: Large for gestational age, SAR: Specific absorption rate

pregnancy and the duration of time spent on the phone are shown in Table 3. Although both phone SAR values and the time spent on the phone were higher in the symmetrical SGA group compared to the asymmetrical SGA group, the difference was not significant (p=0.109 and p=0.162, respectively) (Table 3).

Two hundred four of the babies were preterm. The comparison of the SAR values and time spent on the phone in terms of preterm delivery is shown in Table 4. Both the SAR values and time spent on the phone were higher for the preterm babies compared to the term babies, but again the difference was not significant (respectively p=0.473 and p=0.267) (Table 4).

Discussion

Cell phone use has rapidly increased during the last several decades and the negative effects of RF-EMFs used in cell phone technology on health are a subject of research. RF-EMF exposure during pregnancy has been investigated with conflicting results (2,15). Daşdağ et al. (20) found that the course of pregnancy was not affected by exposure to RF-EMF during pregnancy in rats, but the offspring of the rats exposed to the RF-EMF had lower birth weight. Shirai et al. (21) investigated the effects of an RF-EMF applied to pregnant rats at different frequencies and discovered that it had no negative results on the ongoing pregnancy or offspring of the rats. Yüksel et al. (22) found that RF-EMF exposure could cause low birth weight in rats through increased intrauterine oxidative stress.

Table 2. Gestational age, birth weight, and telephone use data of mothers of SGA and non-SGA babies

Characteristics	SGA babies (n=208) n (%)	Non-SGA babies (n=1287) n (%)	p
Gestational age (weeks)*	39 (37.1-39.8)	39 (38-40)	0.303
Birth weight (grams)*	2200 (2052-2450)	3280 (3015-3560)	0.001
Pre-pregnancy weight (kg) *	63 (49-68)	62 (47-70)	0.997
Weight gain during pregnancy (kg) *	12 (8-16)	12.5 (7.5-17)	0.965
Body mass index*	19.9 (18.7-29.3)	20.9 (18.9-28.8)	0.706
Phone SAR level (W/kg)*	1.42 (1.09-1.49)	1.09 (1.02-1.26)	0.001
Daily time spent on phone (minutes)*	190 (142.5-240)	190 (150-240)	0.969
Physical exercise	Absent: 194 (93.3) Intermittent: 10 (4.8) Regular: 4 (1.9)	Absent: 1206 (93.7) Intermittent: 66 (5.1) Regular: 15 (1.2)	0.962
Education	Illiterate: 1 (0.5) Primary/middle school: 183 (88.0) High school/university: 24 (11.5)	Illiterate: 1 (0.08) Primary/middle school: 1235 (96.0) High school/university: 51 (3.92)	0.671
Socioeconomic status (low)	195 (93.7)	1156 (89.8)	0.077
Smoking during pregnancy	4 (1.9)	7 (0.5)	0.054

*: Median (interquartile range: 25-75), SGA: Small for gestational age, SAR: Specific absorption rate

Table 3. Phone use data of mothers of asymmetrical and symmetrical SGA babies

Characteristics	Babies with symmetrical SGA, (n=79)	Babies with asymmetric SGA, (n=129)	p
Phone SAR level (W/kg)*	1.42 (1.13-1.51)	1.4 (1.07-1.49)	0.109
Daily time spent on phone (minutes)*	210 (150-250)	190 (140-240)	0.162

*: Median (interquartile range: 25-75), SGA: Small for gestational age, SAR: Specific absorption rate

Table 4. Comparison of the SAR values and time spent on the phone in terms of preterm delivery

Characteristics	Preterm babies, (n=204)	Term and post-term babies, (n=1291)	p
Phone SAR level (W/kg)*	1.12 (1.05-1.45)	1.09 (1.02-1.42)	0.473
Daily time spent on phone (minutes)*	200 (160-240)	190 (150-240)	0.267

*: Median (interquartile range: 25-75), SAR: Specific absorption rate

In their animal study Sommer et al. (23) did not detect any harmful effects on the development of the offspring. Mortazavi et al. (24) found that exposure to ionizing radiation during pregnancy did not increase the risk of low-birth weight. Benson and Shulman (25) reported an increase in the frequency of low birth weight infants in regions where there were high levels of natural radiation exposure. Although there are conflicting results in the literature, in the present study the mothers of SGA fetuses were significantly more likely to use cell phones with higher SAR levels.

ROC analysis identified a cut-off value of the SAR level of 1.23 W/kg for giving birth to an SGA baby with 69.3% sensitivity and 73.0% specificity. To the best of our knowledge, our study is the first to determine a cut-off level. Baste et al. (16) reported that medium and high cell phone exposure during pregnancy decreased the risk of preeclampsia but this was not consistent with the other findings of the present study. Since preeclampsia is a factor known to affect the birth weight of newborn babies, we excluded all pregnant women with any pregnancy complications, including preeclampsia, from the study. Therefore, we were unable to make a comparison regarding the effect of SAR value on the development of preeclampsia.

Nagaoka et al. (12) found that the SAR level to which the fetuses were exposed was lower than that to which the pregnant women were exposed. In addition, Luo et al. (14) found that RF-EMF exposure may change the protein structure of the chorionic villi during early pregnancy, which is the most sensitive stage of intrauterine life, and could affect cell proliferation. Although the difference was not significant, in our study the mothers of babies with symmetrical SGA were found to have used cell phones with higher SAR levels and spent more time on the phone during pregnancy than the mothers of babies with asymmetrical SGA. This finding supports the suggestion that SAR exposure in early pregnancy may cause the development of symmetrical SGA.

Tsarna et al. (2) stated that cell phone use during pregnancy might be associated with the likelihood of preterm delivery. This is supported by the findings reported by Col-Araz (15). These findings are not consistently reported, with Baste et al. (16) finding no association between cell phone exposure and preterm delivery. In the present study, although both the SAR values of phones used during pregnancy and the duration of phone use were higher in preterm deliveries compared to term deliveries, the difference was not significant.

It was planned to investigate the association between the SAR levels of phones used during pregnancy and the duration of cell phone use and the stillbirth rate. However, this evaluation was not possible as the number of stillborn babies was low in our study.

Shen et al. (26) found a rate of SGA births of 5.74%, whereas in the present study, this rate was higher (13.9%). We attribute this difference to the fact that our hospital was a tertiary healthcare institution and that more complicated cases were referred to our hospital. In our study, the median time spent on the phone by the pregnant women was 190 minutes. As the time spent with devices using RF-EMFs increases day by day, more research is required on this issue.

Study limitations

One limitation of our study is that the pregnant women could not be examined in two groups according to less time and more time spent on the phone because of the generally long cell phone daily use time. The retrospective design of our study is the other limitation. Prospective studies with a large number of cases and comparing the effects of SAR levels according to the periods of pregnancy (first, second, and third trimester) are warranted.

Conclusion

As the SAR levels of cell phones used during pregnancy increased, the likelihood of giving birth to an SGA baby increased significantly. ROC curve analysis identified a SAR cut-off value of 1.23 W/kg with 69.3% sensitivity and 73.0% specificity. However, there was no effect on the likelihood of SGA in terms of time spent on the phone in this population.

Ethics Committee Approval: *The KTO Karatay University of Ethics Committee provided ethical approval for the present research (approval number: 2021/019, date: 09.02.2021).*

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

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

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Evaluation of concordance between loop electrosurgical excisional procedure and cervical colposcopic biopsy results

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Abstract

Objective: To evaluate the results of loop electrosurgical excisional procedures (LEEP) with colposcopic biopsy results of patients who presented to our hospital for vaginal smears.

Material and Methods: The LEEP reports of patients who presented to our gynecology clinic between January 2015 and December 2020 were retrospectively evaluated. The data were obtained from electronic patient records and the department of medical pathology archives.

Results: A total of 579 patients were evaluated with a mean age of 38.05±6.17 years. Colposcopy-guided biopsy was not taken from 102 patients. The results of the remaining 477 (82.4%) patients were: no dysplasia (n=12; 2.1%), Cervical intraepithelial neoplasia-I (CIN-I) (n=99; 17.1%), CIN-II (n=111; 19.2%), CIN-III (n=248; 42.8%), and cancer (n=7; 1.2%). Completed excision was performed in 87.0% of the patients using LEEP, the lesion was positive at the surgical margins in 10.9%, and the lesion could not be completely excised in 2.1%. The complication rate after LEEP was 3.1% including pelvic pain (n=5; 0.9%) and bleeding (n=13; 2%). The histopathologic results of LEEP were: benign (n=50; 8.6%), CIN-I (n=110; 19.0%), CIN-II (n=89; 15.4%), CIN-III (n=280; 48.4%), cancer (n=7; 1.2%), and metaplasia (n=37; 6.4%). The concordance between colposcopic biopsy and LEEP results was 85.9% for CIN-I, 71.2% for CIN-II, 98.4% for CIN-III, and 85.7% for cancer diagnoses.

Conclusion: LEEP is a simple minimally invasive method used in the treatment of CIN, with low persistence, recurrence, and complication rates and increased human papillomavirus clearance in most patients. Our results support the consistency of cervical colposcopic biopsy and LEEP results. (J Turk Ger Gynecol Assoc 2024; 25: 13-7)

Keywords: Biopsy, cervical intraepithelial lesion, colposcopy, LEEP

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Introduction

Cervical cancer is the second most common malignancy worldwide, after breast cancer. A woman's risk of developing cervical cancer is 0.8% in developed countries and 1.5% in developing countries. Cervical screening aims to diagnose and treat asymptomatic, precancerous lesions and reduce mortality and morbidity (1). There are more than 100 subtypes of human papillomavirus (HPV) that cause precancerous lesions, about 40 of which are sexually transmitted and infect the skin and mucous membranes. HPV infections are usually temporary in young women under the age of 30 years and are cleared by the immune system. Therefore, HPV testing is not recommended for women aged under 30 years (2).

Cervical intraepithelial neoplasia (CIN) is a premalignant, squamous lesion of the uterine cervix diagnosed through histopathologic evaluation of cervical biopsy material (3,4).

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Proper management of CIN is challenging because any delay in treatment increases the risk of cervical cancer, and overtreatment can cause morbidity in child-bearing, such as preterm delivery, premature rupture of the membrane, and low birth weight (3,5). The two main management approaches for CIN are observation (cervicovaginal cytology and colposcopy) and local excision or ablation of the cervical transformation zone; hysterectomy is not considered the primary treatment (6,7).

The risk of CIN progression to invasive cancer is related to age and grade (low-risk in CIN-I, high-risk in CIN-II or III), with the majority of lesions regressing spontaneously in women aged under 25 years (3,6). In CIN-I under 25 years of age, management is usually in the form of observation, and the follow-up of these patients depends on the previous cytology results (2,6). Annual cervical cytology is recommended for atypical squamous cells of undetermined significance (ASC-US) and low-grade squamous intraepithelial lesions (LSIL), and annual cytology and colposcopy are recommended for high-grade squamous intraepithelial lesions (HSIL), and atypical squamous cells when HSIL cannot be excluded (ASC-H) (4,8). For CIN-II under the age of 25 years, observation or treatment can be recommended, based on the patient's desire for children (6). Annual HPV testing is recommended for CIN-I lesions in women aged over 25 years, and treatment can be recommended for patients who have completed their fertility and whose follow-up will be difficult. Excision or ablation therapy is recommended for CIN-II and III (8). In pregnant women, colposcopic evaluation at the postpartum sixth week is recommended for CIN-I, and cytology and colposcopic evaluation for each trimester for CIN-II and III are recommended. An endocervical biopsy is strictly contraindicated and treatment is required only in the presence of invasive cancer (6). HPV vaccines have no therapeutic effect on CIN and they have only been shown to reduce recurrence (8).

There are two types of treatment for CIN, depending on the degree of the disease; local ablative treatment or excision. Knife cone excision and radical diathermy are traditional methods and are performed under general anesthesia, whereas excisional procedures such as local ablative methods and loop electrosurgical excisional procedures (LEEP) can be performed under local anesthesia in outpatient clinics. The transformation zone of the cervix should be fully visualized and there should be no invasive or glandular disease in local ablative treatment. Excisional treatment is mandatory in case of insufficient colposcopic findings, and invasive and glandular disease (6). Currently, excisional methods with low morbidity, such as laser conization and large loop excision of the transformation zone (LLETZ in the United Kingdom) or LEEP (in the United States) are preferred instead of destructive ablative methods (6,8). Excisional methods allow the complete removal of the transformation zone of the cervix and a more accurate histopathologic examination of the tissue obtined compared with ablative methods (8).

In this study, the aim was to evaluate the LEEP results of 579 patients who presented to our hospital for vaginal smears between 2015 and 2020.

Material and Methods

Patients who underwent biopsy between January 2015 and December 2020 after colposcopic examination for suspicious CIN in whom LEEP was performed were included. Ethical approval was obtained from the institutional review board of Necmettin Erbakan University Faculty of Medicine (approval number: 2021-3429, date: 01.10.2021). The data were reviewed from electronic patient records and the medical pathology department archives. Informed consent was obtained from all patients included in the study at the time of their first admission to the clinic for future use. The samples obtained from LEEP were evaluated by two certified and experienced senior histopathologists. The data, including the patient age, menopausal status, smear results, colposcopic biopsy results, HPV test results before and after LEEP, surgical procedure results, histopathological results of LEEP, complications after LEEP, follow-up time, disease course, and recurrence were recorded and analyzed. The exclusion criteria were patients who had previously been treated for CIN, inadequate colposcopic findings, and incomplete records.

The results of cervical cytology (our center or externally referred) of patients were assessed according to the Bethesda 2014 classification. The colposcopic evaluation was performed using a Carl Zeiss (Oberkochen, Germany) colposcopy device by two experienced gynecology-oncology specialists who had received colposcopy training, and biopsies were taken from the lesion and/or suspicious areas using Tischler biopsy forceps. Endocervical curettage was also routinely performed after the cervical biopsy procedure. The samples were fixed with formalin for histopathological evaluation and sent to the histopathology department.

LEEP was performed in cases of a CIN-II and CIN-III detection in colposcopic biopsy and/or with a strong CIN appearance in colposcopy or cytology, even if the biopsy result was normal, or if the transformation zone could not be seen under sedative anesthesia. LEEP was performed in some patients who completed their fertility after recurrent abnormal smears without high-risk suspicion at their request. In the case of suspected endocervical disease, LEEP was performed separately for the vaginal part and the intracervical part of the cervix. The lesion and/or transformation zone was excised using a 15-25 mm round loop electrode (50-60 W). After the

tissue of the suspicious or visible lesion was excised, the safe depth of field was determined as 6 mm. Bleeding control after LEEP was performed using a ball-tipped monopolar electrode. The patients were re-evaluated 3-6 months after the procedure for persistent disease with cytology, HPV test, colposcopy, and, if necessary, cervical biopsy and/or endocervical curettage. All procedures were conducted in accordance with the 2019 American Society for Colposcopy and Cervical Pathology Risk-Based Management Consensus Guidelines (9).

Statistical analysis

Data were analyzed using the SPSS, version 15.0 for Windows (SPSS, Chicago, IL, USA). Continuous variables are expressed as mean ± standard deviation. Nominal data are expressed as the number of patients and percentages.

Results

Eighty-six of the 665 patients who were reviewed between January 201 and December 2020 were not eligible and were excluded from the study [previously treated; (n=26), inadequate colposcopic findings; (n=34), and incompleted patients record; (n=26)]. The remaining 579 patients were analyzed in this retrospective study.

Table 1 lists the detailed characteristics of the patients. The mean age of the patients who underwent LEEP was 38.05±6.17 and 61 patients (10.5%) were menopausal. The results of cervical cytology on admission were: atypical squamous cell of undetermined significance (ASC-US), n=65 (11.2%); LSIL, n=116 (20.1%); HSIL, n=316 (54.5%); ASC-H, n=64 (11.1%); and atypical glandular cells (AGC), n=18 (3.1%). Colposcopic biopsy was not performed in 102 patients (17.6%) due to a strong CIN appearance on colposcopy and/or the transformation zone could not be seen. The remaining 477 colposcopy biopsy results were: no dysplasia (n=12; 2.1%), CIN-I (n=99; 17.1%), CIN-II (n=111; 19.2%), CIN-III (n=248; 42.8%), and cancer (n=7; 1.2%). The HPV positivity rate was 83.2% before LEEP, and this rate decreased to 18.7% in the post-procedure follow-ups. Completed excision was performed in 87.0% of the patients who underwent LEEP; lesions were positive at the surgical margins in 10.9% and the lesions could not be completely excised in 2.1%. The procedure was repeated in eight of 12 patients whose lesions could not be completely excised while the other four patients underwent close follow-up. The complication rate after LEEP was 3.1% which included pelvic pain n=5 (0.9%) and bleeding n=13 (2%). Four of the patients with bleeding were cauterized using monopolar cauterization, three were cauterized with silver nitrate, and hemostasis was achieved with sutures in six. The histopathologic results after LEEP were: benign outcome (n=50; 8.6%); CIN-I (n=110; 19.0%); CIN-II (n=89; 15.4%); CIN-III (n=280; 48.4%); cancer

Table 1. The characteristics of the patients

Features		Mean ± SD	n	%
Age (years)		38.05±6.17		
Premenopause			518	89.5
Postmenopause			61	10.5
Cervical cytology resultson admission	ASC-US		65	11.2
	L-SIL		116	20.1
	ASC-H		64	11.1
	H-SIL		316	54.5
	AGC		18	3.1
Colposcopic biopsy results	No dysplasia		12	2.1
	CIN-I		99	17.1
	CIN-II		111	19.2
	CIN-III		248	42.8
	Cancer		7	1.2
	Not performed		102	17.6
Before LEEP HPV testing	HPV (+)		482	83.2
	HPV (-)		97	16.8
LEEP result	Completed excision		504	87.0
	Incomplete excision		12	2.1
	Ambiguous appearance		63	10.9
Histopathological results of the LEEP	Benign		50	8.6
	CIN-I		110	19.0
	CIN-II		89	15.4
	CIN-III		280	48.4
	Cancer		13	2.2
	Metaplasia		37	6.4
Complications	None		561	96.9
	Pelvic pain		5	0.9
	Bleeding		13	2.2
Follow-up time (months)		37.2±15.1		
HPV testing after LEEP	HPV (-)		471	81.3
	HPV (+)		108	18.7
Disease course	No persistence		563	97.2
	Persistence		16	2.8
Recurrence	No		575	99.3
	Yes		4	0.7

ASC-US: Atypical squamous cell of undetermined significance, L-SIL: Low-grade squamous intraepithelial lesion, ASC-H: Atypical squamous cells-HSIL cannot be excluded, H-SIL: High-grade squamous intraepithelial lesion, AGC: Atypical glandular cells, CIN: Cervical intraepithelial neoplasia, LEEP: Loop electrosurgical excisional procedure, HPV: Human papillomavirus, SD: Standard deviation

Table 2. Concordance of colposcopic biopsy and LEEP results of the patients

Colposcopic biopsy results, (n=579)	LEEP results, (n=579)					
	No dysplasia, (n=50)	CIN-I, (n=110)	CIN-II, (n=89)	CIN-III, (n=280)	Cancer, (n=13)	Metaplasia, (n=37)
No dysplasia, (12) (%)	10 (83.3)	-	-	-	-	2 (16.7)
CIN-I, (99) (%)	3 (3.0)	85 (85.9)	5 (5.1)	3 (3.0)	-	3 (3.0)
CIN-II, (111) (%)	2 (1.8)	14 (12.6)	79 (71.2)	13 (11.7)	1 (0.9)	2 (1.8)
CIN-III, (248) (%)	-	1 (0.4)	-	244 (98.4)	3 (1.2)	-
Cancer, (7) (%)	-	-	-	1 (14.3)	6 (85.7)	-
No performed, (102) (%)	35 (34.4)	10 (9.8)	5 (4.9)	19 (18.6)	3 (2.9)	30 (29.4)

LEEP: Loop electrosurgical excisional procedure, CIN: Cervical intraepithelial neoplasia

(n=7; 1.2%); and metaplasia (n=37; 6.4%). The mean follow-up period of the patients was 37.2+15.1 months with persistent disease in 16 (2.8%) and recurrence in four (0.7%).

The concordance of the colposcopic biopsy and LEEP results of the patients is presented in Table 2. In the LEEP results of 12 patients without dysplasia in the colposcopic biopsy, metaplasia was reported in two. Of 99 patients with CIN-I detected in colposcopic biopsies, 85 had CIN-I, five had CIN-II, and three had CIN-III after LEEP. The LEEP results of 111 patients diagnosed as having CIN-II in colposcopic biopsies were reported as CIN-II in 79 patients, CIN-I in 14, and cancer in one patient. Of the 248 patients in whom preoperative CIN-III was detected on colposcopic biopsy, CIN-III was found in 244, CIN-I in one, and cancer in three patients. Seven patients were diagnosed as having cancer through colposcopic biopsies, cancer was reported again in six patients, and CIN-III was reported in one patient after LEEP. Of 102 patients without preoperative biopsies, no dysplasia was observed in 35, metaplasia was seen in 30 patients, CIN-III was found in 19 patients, CIN-I was seen in 10 patients, CIN-II was seen in five patients, and cancer in three patients on histopathologic evaluation after LEEP. Concordance between colposcopic biopsy and LEEP were 85.9% for CIN-I, 71.2% for CIN-II, 98.4% for CIN-III, and 85.7% for cancer diagnoses; the overall concordance for all lesions was 73.2%.

Discussion

The current study presents the results of 579 women who underwent LEEP with suspicion of CIN, showing that completed excision was performed in 87.0%, the complication rate was 3.1%, the persistence rate was 2.8%, the recurrence rate was 0.7%, and the concordance between colposcopic biopsy and LEEP results was 85.9% for CIN-I, 71.2% for CIN-II, 98.4% for CIN-III, and 85.7% for cancer diagnoses. The overall concordance for all lesions was 73.2%.

LEEP, which was first tried in 1986, is now a highly effective, safe, and tolerable surgical procedure in the treatment of CIN. Published studies have shown that the rate of persistence of disease is between 2-5% and the rate of recurrence is between 0.5-4% (3,10). The reason for these differences in rates is due to the difference in the surgical confidence intervals and therefore the depth of resection. In addition, LEEP has higher efficiency and lower complications compared with cold knife conization and can be performed under local anesthesia in outpatient clinic conditions. It is quite easy to remove lesions or the transformation zone of the cervix with the loop electrode because it is made of thin tungsten or steel wire (8). In the present study, the persistence rate was 2.8% and the recurrence rate was 0.7%, which is consistent with the published data. The most prominent complication of LEEP are postoperative bleeding and pain and are reported to vary between 2-4% and 0.5-2%, respectively (3,11-13). In the present study, our complication rate was 2.2% for vaginal bleeding affected 2.2% and 0.9% of patients reported pain, again consistent with the literature.

Known risk factors for persistence and recurrence of CIN are the presence of positive surgical margins and HPV infection. It has been reported that the majority of HPV infection after LEEP is cleared and the HPV positivity rate after surgical procedures varies between 10-25% (3,14,15). In the present study, an HPV test was performed during the postoperative follow-up of the patients, and the HPV positivity after LEEP results was 18.7%, consistent with the literature.

There are no clear data concerning the concordance of LEEP results and colposcopic biopsy results. In previous studies, the concordance of colposcopic biopsy and LEEP results varies between 60-85% in LSIL and 80-95% in HSIL (3,16-20). In accordance with this,found concordance of around 80% for LSIL and 90% for HSIL. The reason why LSIL is lower than HSIL may vary in the histopathological diagnosis of LSILs, while this variability is lower in HSIL (3). Another reason for the high concordance in our study may be that colposcopic procedures were performed by two experienced and trained gyneco-oncologists, and colposcopic biopsies and LEEP were performed in the same center. The number of patients

diagnosed as having CIN-II through colposcopic biopsy decreased on definitive histopathological diagnoses after LEEP in our study. This may hve occurred because of removal of the dysplastic lesion by biopsy or its spontaneous regression. The low recurrence rate and the decrease in the HPV positivity rate may also have been due to these causes.

Study Limitations

The limitations of the study were that it was retrospective and performed in a single tertiary center. On the other hand, a strength was that cervical colposcopic biopsy and LEEP were performed by the same gyneco-oncologist. In addition, the evaluation of the samples by two histopathologists who were experienced and trained in the field of oncology is another positive feature of our study.

Conclusion

LEEP is an easy-to-use, minimally invasive method used in the treatment of CIN, with low persistence, recurrence, and complication rates, and increased HPV clearance in most patients. Our results show very acceptable concordance between cervical colposcopic biopsy and LEEP results.

Ethics Committee Approval: *Ethical approval was obtained from the institutional review board of Necmettin Erbakan University Faculty of Medicine (approval number: 2021-3429, date: 01.10.2021).*

Informed Consent: *Informed consent was obtained from all patients included in the study at the time of their first admission to the clinic for future use.*

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

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Demographic distributions and clinical results of assisted reproduction techniques in Turkey in 2019: a descriptive survey

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Abstract

Objective: The aim of this study was to describe characteristics and outcomes of assisted reproductive technology (ART) cycles performed in 2019 in Turkey.

Material and Methods: One-hundred and sixty-five ART centers in Turkey were invited to submit data. The survey was sent to center directors via e-mail with anonymous links by Qualtrics™. The survey involved questions about their patient characteristics, clinical practices, and outcomes.

Results: Forty-one (24.8%) centers responded to e-mails, and data gathered from 25 centers was included in the analyses. In 25 centers, 18,127 fresh or frozen transfers were carried out during the study period, of which 7796 (43.0%) were fresh and the rest were either frozen (45.2%) or embryo transfers (ET) with preimplantation genetic testing (PGT) (11.8%). The live birth rate per ET was as 30.6%, 40.1%, and 50.7% in fresh, frozen and PGT cycles, respectively. A single embryo was transferred in 65.3% of all transfers and singleton live births comprised 86.1% of all deliveries. For cycles with intrauterine insemination, 1407 were started in 2019, and 195 clinical pregnancies, 150 live births with 19 multiple pregnancies occurred. A total of 1513 ART cycles were initiated for foreign patients. Russia (29.6%), Germany (7.4%), Iraq (4.6%), Uzbekistan (3.1%), and Syria (1.4%) were the top five countries with most patients coming to Turkey for ART.

Conclusion: The survey results are in parallel with the reports of international institutions and organizations. With repeated editions, the data collected with annual surveys can be used to inform ART practices in the coming years. (J Turk Ger Gynecol Assoc 2024; 25: 18-23)

Keywords: Assisted reproduction technology, medically assisted reproduction, in-vitro fertilization, embryo transfer

Introduction

Assisted reproductive technology (ART) is a widely used and highly effective treatment for infertility. However, a comprehensive national registry is required to audit ART outcomes properly. The absence of publicly available national data concerns patients, providers, and researchers and is needed to understand the success rates and safety of ART practice in any jurisdiction.

Annual reports on ART help provide reliable and aggregated data to inform healthcare policies, enable calculation of associated costs, facilitate the development of and access to treatment and increase the quality of care provided. Among such national and international registries are the ones managed by the Centers for Disease Control and Prevention and Society for Assisted Reproductive Technology (SART)/American Society of Reproductive Medicine in the USA, by the Human Fertilization and Embryology Authority (HEFA) in the UK and by European Society of Human Reproduction and Embryology (ESHRE) in the Europe an Community (1-3).

Information provided by these registries contributes to significant improvements in ART practice. A noteworthy example is limiting the number of embryos transferred. The common practice of multiple embryo transfers (ET) and advances in embryology laboratory procedures in the 1990s resulted in an increased incidence of multiple pregnancies. As a result, ART pregnancies were associated with increased maternal/antenatal morbidity. Increased awareness provided by the registries prompted mandatory, as well as voluntary, decreases in the number of embryos transferred.

Continuous effort is required to optimize data collection in order to enhance surveillance and quality assessment in ART. Standardized annual reports would help identify areas for improvement. In addition, transparency of national ART statistics may help international patients seeking treatment in a particular country.

The aim of the current multicenter, descriptive survey was to describe demographic distributions and clinical results of ART cycles in Turkey in 2019 through aggregated, anonymized data.

Material and Methods

An invitation e-mail (Supplement 1) was sent to clinic directors in public and private ART centers. The mailing list was created by combining the shared communication lists of non-profit associations operating in our country, such as the Turkish Reproductive Health and Infertility Association (TSRM), the Clinical Embryology Association and the In-Vitro Fertilization (IVF) Centers Association. If a center did not respond within a week, a repeat e-mail was sent. For those centers with telephone number information, a reminder call was placed. Data were collected in an anonymized manner at both clinic and individual patient level.

The questionnaire followed the template of the ESHRE [European IVF Monitoring (EIM)] consortium. It included an online informed consent form for the clinic directors, with an invitation statement from the survey's principal investigator, and a brief explanation of the purpose. It was stressed that participation was voluntary and that the responses would remain anonymous. The survey inquired about data for the year 2019.

The survey was prepared with Qualtrics™, an internet-based commercial survey system. The survey consisted of 12 question blocks, including preliminary information with 25 questions (Supplement 2). The survey was designed using a set of validated benchmarks in line with the training videos suggested by Qualtrics™. Artificial intelligence-assisted adaptive inquiry methods created by Qualtrics™ were used to lessen the question counts and, where applicable, the complexity

of the items. To prevent multiple data submissions by the same participant, Qualtrics™ places a cookie in participants' browsers when they submit a response. All security measures offered to the Qualtrics™ users can be accessed from the links in supplementary files. Qualtrics™ is ISO 27001, 27017, and 27018 certified and is a FedRamp (US government security compliance standard with over 300 audits based on the highly respected NIST 800-53 that requires ongoing monitoring and periodic independent reviews) (4).

The projected study duration was 60 days, with estimations of 15 days for volunteers to fill out the survey, 10 days for data collection and analysis, five days to apply the preliminary analysis and share the initial report with the participants, and 30 days to perform the final analysis and compose the manuscript.

Definition of terms used in the survey

The parameters for documenting ART treatment outcomes were defined as the standards set by World Health Organization/ International Committee for Monitoring Assisted Reproductive Technologies (WHO/ICMART). To illustrate, clinical pregnancy is defined as ultrasonographic confirmation of one or more gestational sacs or definitive clinical signs of pregnancy, while delivery is defined as live and/or stillbirth occurring after the 22nd gestational week. The live birth rate (LBR) per ET was defined as the ratio of ETs to the number of births, irrespective of the number of babies born or the number of embryos transferred. Preterm delivery was defined as births before 37 weeks of gestation, late preterm as births between 32 and 37 weeks and very preterm deliveries as births before 32 weeks of gestation. All the terms were based on WHO/ICMART definition and explained above in the appropriate question blocks in the survey (5). Ovarian hyperstimulation syndrome (OHSS) was defined and staged according to the Practice Committee of the American Society for Reproductive Medicine guideline on OHSS in 2016 (6).

The study was approved by the Koç University Ethics Committee (approval number: 2022.386.IRB1.141, date: 07.11.2022). The authors confirm that fully informed, freely given and written consent to participate were obtained from all participants (cohort) in the present study.

Statistical analysis

As this was a descriptive study, only measures of frequency (count, percent, and frequency) were used, and no comparative statistical analyses were conducted.

Results

The survey was sent to the directors of 165 ART centers via e-mail with anonymous links provided by Qualtrics™. Of these, 41 (24.8%) replied and 26 (15.76%) completed the questionnaire. Data from 25 (15.15%) centers that answered more than 50% of the questions were included in the report. Figure 1 shows annual ART cycles carried out during the study period.

Overall results per ART cycle

The results based on the stage (cleavage, blastocyst) or the number of the transferred embryos in the fresh or frozen cycles and the distribution according to the patient's age at oocyte-pickup and gestational age at delivery are shown in Figure 2, Figure 3a-c), respectively. Additional characteristics of the (a)

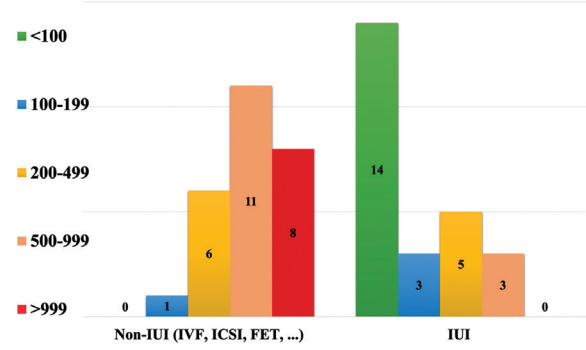

Figure 1. Distribution of clinics by the number of cycles they performed in 2019
IUI: Intrauterine insemination, IVF: In-vitro fertilization, ICSI: Intracytoplasmic sperm injection, FET: Frozen-embryo transfer

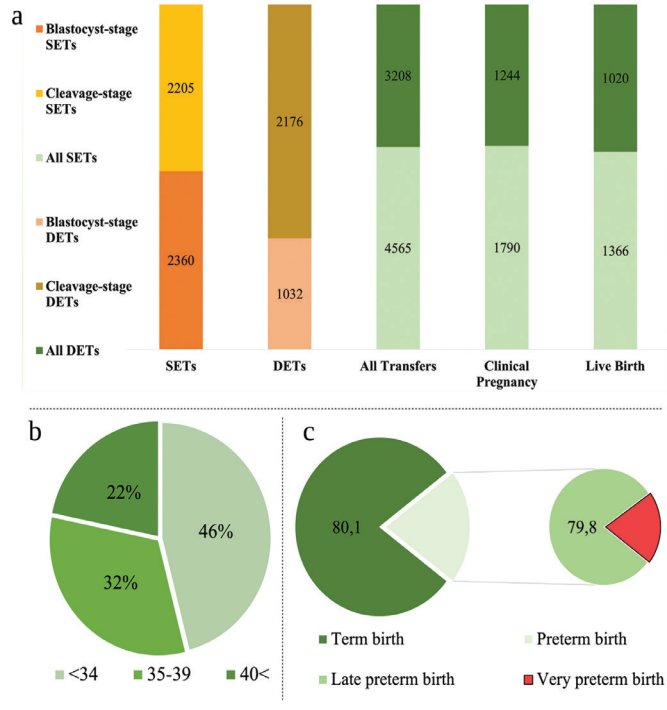

Figure 2. Distributions and clinical outcomes by (a) transferred embryo number/stage, (b) age and (c) birth week in fresh cycles
SET: Single embryo transfer, DET: Double embryo transfer

fresh, (b) frozen or (c) preimplantation genetic test (PGT) transfers are presented in Figure 4.

Intrauterine insemination

A total of 1407 intrauterine insemination (IUI) procedures were performed in 25 centers in 2019. Women were younger than 35 years in 80.9%, between 35 and 39 years old in 16.3% and 40 years or older in 2.8% of cycles. Of these, 195 cycles (13.8%) resulted in clinical pregnancy, and 150 (10.6%) resulted in delivery. Of all births, 15 resulted in twin pregnancies and four were higher order. Pregnancy outcomes were not available for six cycles.

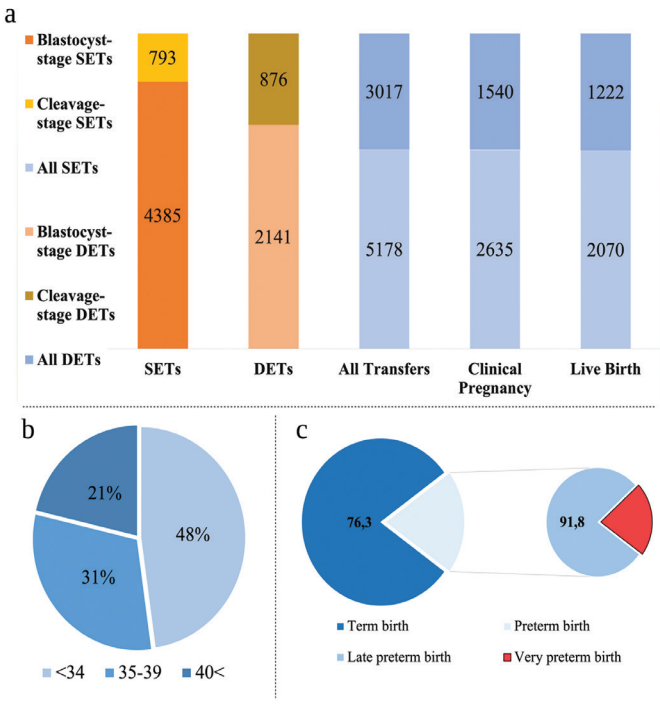

Figure 3. Distributions and clinical outcomes by (a) transferred embryo number/stage, (b) age and (c) birth week in frozen cycles
SET: Single embryo transfer, DET: Double embryo transfer

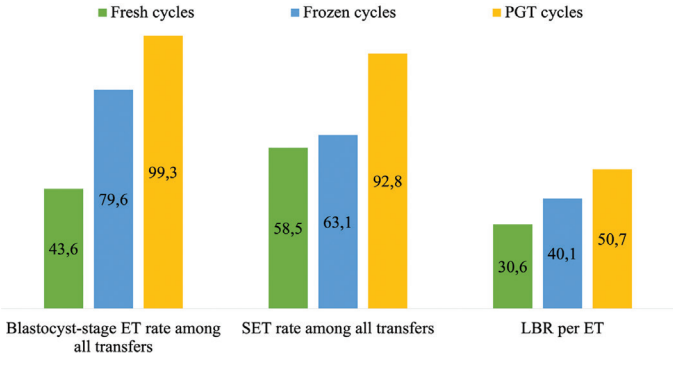

Figure 4. Transfer characteristics and results in Fresh, Frozen and PGT cycles
ET: Embryo transfer, SET: Single embryo transfer, LBR: Live birth rate, PGT: Preimplantation genetic test

Fresh cycles

In the 25 clinics included in the survey data, 11,121 oocyte pick-ups (OPU) were conducted, and following IVF or intracytoplasmic sperm injection (ICSI), 7796 fresh ET procedures were performed. In 2696 cycles, sperms were obtained by surgical procedures [testicular sperm extraction (TESE), micro-TESE, or fine needle aspiration]. A single embryo was transferred in 4565 (58.5%) fresh transfers, and in 3208, double embryos were transferred. Data for 23 transfers were missing. Of all fresh transfers, 626 resulted in pregnancy loss, 3036 (38.9%) resulted in clinical pregnancy, 2388 (30.6%) ended in a live birth, 279 of which were twin or higher-order pregnancies. Pregnancy outcomes of 22 cycles were missing.

Frozen cycles

These consisted of 8433 thawings and 8197 transfers were performed, of which 5178 (63.1%) were single ETs. Data for two transfers were missing. Among all frozen cycles, 811 resulted in pregnancy loss, 4177 (50.9%) resulted in clinical pregnancy, and 3294 (40.1%) in a live birth, 449 of which were twin or higher-order pregnancies. Pregnancy outcomes of 72 cycles were missing.

Cycles with PGT

In the survey, information was not requested about the platform used for genetic analysis in the PGT procedure (comparative genomic hybridization, single-nucleotide polymorphism, next-generation sequencing arrays) or on the reported result of PGT, for example whether mosaicism was reported, or which embryos were transferred in the presence of mosaicism. Therefore, the results should be interpreted cautiously in the absence of these details. Nevertheless, according to the data from the 25 centers, 1252 (58.6%) clinical pregnancies after 2134 ETs were achieved, of which 1083 (50.7%) resulted in a live birth. In addition, 130 women experienced pregnancy loss, and pregnancy outcomes of 39 cycles were missing.

Complications during ART applications and fetal reduction procedures

Seventy-three women were reported to require hospitalization for stage 3 or above OHSS. Data for complications due to OPU procedures that resulted in hospitalization were also collected. Moreover, 55 women were hospitalized due to bleeding, eight because of infection and two for other causes. None of these resulted in death. A total of 15 fetal reduction procedures were performed in the 25 centers in 2019.

Data from international patients

Nine centers completed the question block about couples who did not reside in Turkey but were undergoing ART treatment here. A total of 1552 cycles were performed [83.6% only IVF or ICSI, 16.4% pre-implantation genetic diagnosis (PGD)]. The top five countries where these couples reside were Russia (29.6%), Germany (7.4%), Iraq (4.6%), Uzbekistan (3.1%), and Syria (1%). The remaining 851 couples (56.2%) were from other countries. The reason for choosing a foreign country for treatment was enquired about. According to the survey, only 68 (4.4%) couples chose Turkey because of the treatment cost benefit.

Discussion

This was a descriptive survey study including data from 25 infertility centers operating in Turkey with data collected for the year 2019. Our purpose was not to compare centers or treatment modalities but to provide an overview of demographic properties and ART treatment in Turkey, using anonymous data. According to the Turkish Statistical Institute, women of reproductive age (between 15-45 years old) make up 26.5% of the population in Turkey, and 1,194.423 births took place in 2019 (7). In the same year, a total of 18,127 ETs were carried out in 25 centers, and 43.0% of these transfers included fresh, 45.2% frozen cycles, and 1.8% PGT cycles. In total, 64.6% ETs were single ETs and the singleton LBR among all deliveries was 87.5%. As for the IUI cycles in the same year, 1407 cycles were initiated and there were 195 clinical pregnancies and 150 deliveries occurred.

As demonstrated in international reports, ART applications has increased compared to prior years (1,2). To exemplify from (HFEA) data, the number of cycles, around 30,000 in the 90s and 40,000 in the early 2000s, is approaching approximately 70,000 in 2019 (1). Although the ultimate success of ART/MAR treatments is expressed as the take-home baby rate, the treatment processes must be within the scope of excellence and ethical health care, without increasing maternal and antenatal morbidity. In this context, annual international statements are imperative to regulate treatment planning.

In 2021 and 2022, annual reports for 2019 on infertility treatments applied in the United Kingdom and the United States were published by HFEA and SART, respectively (1-3). According to SART reports, when all cycles other than donation cycles are considered, LBRs per egg collection attempt in patients under 35 years old, 35-37 years old, 38-40 years old, 41-42 years old and over 42 years old, were 55%, 41%, 26.8%, 13.4%, and 4.3%, respectively. Of these deliveries, preterm delivery rates varied between 12.3% to 15.7% which is lowest in women under 35 years old and highest in women over 42 years old. Finally, the number of transferred embryos varies between 1.2 (under 35 years old) and 2.1 (over 42 years old) (2). In the present study we could not analyze transferred embryo or gestational week at delivery according to different age groups. However, the LBR per aspiration in fresh cycles was 28.5% in women under 35 years of age, 20.3% in the 35-39 age group, and 7.5% for >40 years group. The LBR per thawings in frozen cycles was 45.4% in women under 35 years of age, 40.7% in the 35-39 age group, and 22.3% for >40 years group. According to the HFEA report relating to the same year, LBRs per ET in different age groups ranged from below 5% (43 years and above) to 32% (under 35 years old). Other important points in the HFEA report were that single ET constituted 75% of all transfer cycles, multiple births were reduced to 6% of all births (28% in the 1990s), and patients over 40 years of age have a rate of 21% in all cycles (almost doubled compared to 1990s) (1). In the present study, we found that the single ET rate was 65.3% of all cycles, and the multiple birth rate was 13.9% among all deliveries.

In these annual reports, it is crucial to demonstrate to what extent or rate ART treatments are covered by private insurance or the national social healthcare system. For example, US national-registry ART practices data revealed significant discrepancies in outcomes based on state-obliged policies and insurance treatment coverage rates. Compared with states without compulsory insurance coverage for ART, states with comprehensive jurisdiction have lower rates of multiple pregnancies (especially three or more) and fewer ET per cycle (8,9). As an explanation for these statements, it was presumed that in states where treatment costs are not required to be covered, it is a challenge to accomplish a “successful” result from the first time and, therefore, to transfer more embryos per cycle (8). A similar situation can be investigated in Turkey by adding a couple of parameters to the cycle outcomes data collected in upcoming years.

The biggest strength of our study was that, to the best of our knowledge, this study is the first to include a large number of ART centers in Turkey that allows a panoramic view of the status of ART practice through aggregated anonymous data. Next, the survey was prepared in accordance with ESHRE EIM consortium. Moreover, it is a promising start to monitor the trends in ART treatment in Turkey over the upcoming years, if the survey is carried out annually.

Study limitations

The most significant limitation of our study is the low participation rate of around 15%. Other limitations are the scarcity of data for fertility preservation which has gained popularity and the lack of detailed allocation of treatment attributes according to specific age groups, such as the number of transferred embryos, multiple pregnancy rate, and

distribution by the week of birth. We hope to overcome these limitations in future surveys.

Conclusion

This nationwide survey describes the demographic distributions and clinical results of ART practices in Turkey in 2019. Our results are in parallel with those reported by international institutions and organizations. This study is the first step towards developing an annual overview of ART practices in Turkey. We hope it will attract more participants, include more detailed data in the upcoming years and will serve to inform patients, health care professionals working in the field of ART and policymakers and improve ART practice in our country.

Ethics Committee Approval: *The study was approved by the Koç University Ethics Committee (approval number: 2022.386. IRB1.141, date: 07.11.2022).*

Informed Consent: *The authors confirm that fully informed, freely given and written consent to participate were obtained from all participants (cohort) in the present study.*

Author Contributions: *Surgical and Medical Practices: Y.A., M.B., V.B., S.B., A.D., S.D., E.E., N.F., H.G.Ç., İ.G., M.I., S.M., M.Ö., H.Ö., E.Ş., Y.E.Ş., G.U., B.U., K.V., H.Y., B.B., B.A.; Concept: C.B., B.B., B.A.; Design: C.B., B.B., B.A.; Data Collection or Processing: C.B., B.B., B.A.; Analysis or Interpretation: C.B., B.B., B.A.; Literature Search: C.B., B.B., B.A.; Writing: C.B., B.B., B.A.*

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Laparoscopic myomectomy videos on WebSurg and YouTube: does peer review process make a difference?

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Abstract

Objective: This study aimed to evaluate the quality of laparoscopic myomectomy videos on YouTube and WebSurg.

Material and Methods: We searched using the keyword "laparoscopic myomectomy" on WebSurg and selected surgical interventions in the gynecology section. Eleven videos on WebSurg were enrolled. We selected the 22 most-relevant videos on YouTube to create a comparison group, with a ratio of 1:2. Sound in videos, number of subscribers, views, likes, and comments, number of days since videos were uploaded and durations of videos were recorded. View/day, like/view, like/subscriber, and view/subscriber ratios were calculated. The videos were evaluated with usefulness score (US), global quality scoring (GQS), modified discern score (mDS) and laparoscopic surgery video educational guidelines (LAP-VEGaS).

Results: The view/day ratio was lower in WebSurg compared to YouTube [1.3 (1.9) vs. 7.5 (30.6), respectively; p=0.039]. No difference was found between WebSurg and YouTube in terms of US, GQS and mDS. On LAP-VEGaS assessment, WebSurg was found to be superior to YouTube in terms of intraoperative findings [2 (1-2) vs. 1 (0-2), p=0.001], additional materials [1 (0-2) vs. 1 (0-1), p=0.041], audio/written commentary [2 (2-2) vs. 2 (0-2), p=0.037], image quality [2 (2-2) vs. 2 (0-2), p=0.023], questions and total score [12 (11-13) vs. 10.5 (4-13), p=0.006]. The proportion of high-quality video was higher in WebSurg compared to YouTube, when the cut-off value of total score of 11 or 12 was used as 10 (100%) vs. 10 (50%), p=0.011 and 9 (90%) vs. 5 (25%), p=0.001, respectively.

Conclusion: WebSurg was better compared to YouTube in terms of quality of laparoscopic myomectomy videos. (J Turk Ger Gynecol Assoc 2024; 25: 24-9)

Keywords: Laparoscopic myomectomy, YouTube, WebSurg, global quality scoring, LAP-VEGaS

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Introduction

Uterine fibroids are the most common benign gynecological tumors and almost three-quarters of women of reproductive age have fibroids (1). Although there are currently medical and radiological treatment options, surgery is still the most common treatment modality in the presence of appropriate indications. With the development of endoscopic surgery, laparoscopy has been frequently preferred for myomectomy. We speculate that although laparoscopic myomectomy is currently thought of as advanced gynecological surgery, it will probably become a gold-standard in the future with the increase in surgical experience.

During the coronavirus disease-2019 (COVID-19) pandemic, admission of patients was prohibited, except for emergencies, in most hospitals. Many elective surgeries had to be postponed and consequently residents' opportunities to see and perform surgery was limited. There were studies in the literature showing that residents were not satisfied with education during the pandemic (2). Distance learning methods were introduced

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worldwide as a solution and many institutions continued their education online. As a result, the COVID-19 pandemic has shown us the importance and power of distance education (3). YouTube is the most popular video sharing website with over one billion hours of content watched every day by people all around the world (4). Besides music, movies or reality shows, YouTube has a large amount of medical content and is an almost unlimited resource for both healthcare seekers and providers. However, YouTube does not have a standardized peer-review process, which may cause some problems. It is known that a lot of information obtained from the internet is not correct (5). Due to its widespread use, misinformation can be transferred to many people via YouTube. In medicine, this false information transfer has the potential to cause considerable harm.

WebSurg, which was founded in France, is an online university of Research Institute Against Cancers of the Digestive System (IRCAD) (6). WebSurg is a peer-reviewed, distance-learning platform that is freely available and provides information on the latest developments in endoscopic surgery. It would be expected that WebSurg would have more accurate medical information compared to YouTube, as it has content produced and evaluated by a professional team.

YouTube and WebSurg platforms have become popular sources for surgery-related information due to the ease of access to the internet and the belief that audio-visual media enhance the learning process. There are published studies comparing videos on YouTube and WebSurg platforms. In a study evaluating laparoscopic hysterectomy videos, WebSurg was found to be superior to YouTube (7). Similarly, WebSurg was found to be a better platform for laparoscopic gastrectomy videos in terms of educational quality (8). However, in another study on laparoscopic adrenalectomy, YouTube was found to be as useful as WebSurg (9). Therefore, there is no consensus about which of these two platforms is better when used for online learning.

In the literature, there is a notable gap in the existing evidence concerning direct comparison of laparoscopic myomectomy videos on platforms such as WebSurg and YouTube. Furthermore, it has been observed that the assessment of these videos is commonly conducted using a limited set of evaluation scales within published articles. This limitation in the range of assessment tools hinders a comprehensive understanding of the instructional value of these videos for surgical procedures. Addressing these gaps through comparative analysis and diversification of assessment methods could potentially enhance the educational efficacy of these resources and contribute to improved surgical outcomes. Therefore, the aim of the present study was to evaluate and compare the quality of laparoscopic myomectomy videos on YouTube and WebSurg using four different scales.

Material and Methods

In this comparative study, the keyword "laparoscopic myomectomy" was used to search on the WebSurg platform on November 13, 2022 and surgical interventions in the gynecology section were selected, yielding 11 videos from the WebSurg platform. A search with the same keywords was also done on YouTube. We selected the 22 most-relevant videos on YouTube to create a comparison group with a ratio of 1:2. Only surgical videos uploaded by surgeons were included in the study from both platforms. As we used publicly-available data, the ethical approval was not needed.

Two authors (S.C., F.A.) who were senior surgeons with experience in laparoscopy reviewed all videos. Sound in videos, number of subscribers, views, likes, and comments, number of days since videos were uploaded and durations of videos were recorded. The following ratios were calculated: view/day; like/view; like/subscriber; and view/subscriber.

The included videos were categorized into before and after 2019, because 10 steps to be followed in laparoscopic myomectomy were described by Fava et al. (10) in 2019. These steps are surgical preparation, ergonomics/material, preventive hemostasis, hysterotomy, enucleation, bipolar hemostasis, control of missing fibroids, suturing, morcellation/extraction and prevention of adhesions. All included videos were evaluated for the sequential implementation of these steps.

All videos were evaluated and scored by S.C. and F.A. When there was a disagreement, a common score was decided after discussion. The videos were evaluated with usefulness score (US), global quality scoring (GQS), modified discern score (mDS) and laparoscopic surgery video educational guidelines (LAP-VEGaS) video assessment tool. In US, the videos were given a score between 0 and 2 in terms of the presentation of cause, symptom, diagnosis, treatment, recovery and the final score ranged from 0 to 10 (11). The GQS is a five-point scale used to evaluate the overall quality of videos (12). Similarly, videos were scored as 0 (not mentioned) or 1 (mentioned) in terms of clarity, reliability, bias, referencing and uncertainty of content in mDS (13). In both scoring systems, the total score ranged from 0 to 5, and a higher score was associated with better quality. In LAP-VEGaS, there were nine questions about authors/institution information, presentation of the case, position of patient, ports, extraction site and team standardized step by step fashion, intraoperative findings, outcomes of the procedure, additional materials, audio/written commentary and image quality with scores ranging from 0 to 2 for each question (14). In the performance analysis of LAP-VEGaS video assessment tool to determine a quality video, it was suggested that a total score of 11 or higher can be used as a threshold with a sensitivity of 94% and specificity of 73%, while a total score of

12 or higher with a sensitivity of 84% and a specificity of 84%. In our study, total LAP-VEGaS scores were analyzed according to both thresholds.

Statistical analysis

Statistical analysis was performed using SPSS, version 25 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov and Shapiro-Wilk were used to test the normality of the distributions. None of the variables were normally distributed. Ordinal and continuous variables were compared using the Mann-Whitney U test. Pearson's chi-square test or Fisher's exact test were used to compare categorical variables. Median (interquartile range) for continuous values, median (minimum-maximum) for ordinal values and number (percentage) for categorical values are given. A $p<0.05$ was considered statistically significant.

Results

The characteristics of laparoscopic myomectomy videos on WebSurg and YouTube platforms are shown in Table 1. While 80% of WebSurg videos were shared before 2019, only 20% of YouTube videos were published before 2019 (p=0.004). Compared to WebSurg, YouTube videos had more comments [0 (1) vs. 17 (31), respectively; p=0.001]. WebSurg videos were older compared to YouTube videos [4044 (1912.8) vs. 828.5 (970), respectively; p=0.001]. The view/day ratio was lower on WebSurg compared to YouTube [1.3 (1.9) vs. 7.5 (30.6), respectively; p=0.039].

The comparison of US, GQS, mDS and LAP-VEGaS scores of laparoscopic myomectomy videos on WebSurg and YouTube is summarized in Table 2. No difference was found between WebSurg and YouTube in terms of US, GQS and mDS. On LAP-VEGaS assessment, WebSurg was found to be superior to YouTube in terms of intraoperative findings [2 (1-2) vs. 1 (0-2), p=0.001], additional materials [1 (0-2) vs. 1 (0-1), p=0.041], audio/written commentary [2 (2-2) vs. 2 (0-2), p=0.037], questions of image quality [2 (2-2) vs. 2 (0-2), p=0.023] and total score [12 (11-13) vs. 10.5 (4-13), p=0.006]. In addition, the proportion of high-quality video was higher in WebSurg compared to YouTube when the cut-off value of total score of 11 or 12 was used: 10 (100%) vs. 10 (50%), p=0.011 and 9 (90%) vs. 5 (25%), p=0.001, respectively.

Discussion

Our results showed that laparoscopic myomectomy videos on WebSurg were superior to videos on YouTube in terms of intraoperative findings, additional materials, commentary, questions of image quality and total score on LAP-VEGaS assessment. In addition, the percentage of high-quality video was higher in WebSurg compared to YouTube when different cut-off values were used. YouTube has been shown to be a more popular platform compared to WebSurg because the view/day rate of YouTube videos was almost 5.5 times higher than videos on WebSurg.

The COVID-19 pandemic changed many people's behavior, including much more widespread use of online learning techniques. Accessing information through online platforms in order to ensure the continuity of training has been one of the biggest changes (15). Due to the ease of access, online platforms have changed the way surgical education was delivered during the pandemic. In addition, seeing important anatomical structures better, showing the important stages of the surgery by slowing down, and being able to watch the

Table 1. The characteristics of laparoscopic myomectomy videos on WebSurg and YouTube

	WebSurg, (n=10)	YouTube, (n=20)	p
Year			
Before 2019	8 (80%)	4 (20%)	**0.004**
After 2019	2 (20%)	16 (80%)	
Sound			
Didactic voice	10 (100%)	15 (75%)	0.22
Music	0 (0%)	1 (5%)	
None	0 (0%)	4 (20%)	
Number of views*	4682.5 (2699)	5379.5 (35674)	0.69
Number of likes*	65.5 (75)	89.0 (207)	0.66
Number of comments*	0 (1)	17 (31)	**0.001**
Video length (seconds)*	780 (402)	931.5 (659)	0.13
Time passed since upload (days)*	4044 (1912.8)	828.5 (970)	**0.001**
Views/day*	1.3 (1.9)	7.5 (30.6)	**0.039**
Likes/view*	0.01 (0.01)	0.01 (0.01)	0.69

Number [percentage (%)], *Median (interquartile range)

Table 2. The comparison of laparoscopic myomectomy videos on WebSurg and YouTube

	WebSurg, (n=10)	YouTube, (n=20)	p
Usefulness score	3 (2-8)	3 (1-7)	0.59
Global Quality score		4 (2-4)	0.32
Discern score	2(1-3)	3 (1-4)	0.24
LAP-VEGaS score			
Authors/institution information	1 (1-2)	1 (1-2)	0.09
Presentation of the case	1 (0-1)	1 (0-2)	0.71
Position of patient, ports, extraction site and team	1 (1-1)	1 (0-1)	0.30
Standardized step by step fashion	2 (1-2)	2 (1-2)	0.23
Intraoperative findings	2 (1-2)	1 (0-2)	**0.001**
Outcomes of the procedure	0 (0-2)	0 (0-1)	0.65
Additional materials	1 (0-2)	1 (0-1)	**0.041**
Audio/written commentary	2 (2-2)	2 (0-2)	**0.037**
Image quality	2 (2-2)	2 (0-2)	**0.023**
Total score	12 (11-13)	10.5 (4-13)	**0.006**
A total score of 11 or higher*	10 (100%)	10 (50%)	**0.011**
A total score of 12 or higher*	9 (90%)	5 (25%)	**0.001**

Median (minimum-maximum), *Number (%), LAP-VEGaS: Laparoscopic surgery video educational guidelines

videos again when desired are additional advantages of online learning (8,11). In some studies it was shown that distance learning was at least as effective as traditional methods (16). It is obvious that online education is no substitute for training that requires hands-on practice. For this reason, it would be appropriate to use distance education together with classical education methods.

YouTube is the biggest video sharing website in the world. This platform has become a potential source to share health-related contents because it has billions of visitors every day. This situation has also attracted the attention of researchers. Different medical disciplines, such as urology, ophthalmology, orthopedics, endocrinology and radiology have been examining the role of YouTube as a source of medical information (17-21). Another of these disciplines is gynecology. Kaya et al. (11) reported that approximately 20% of the endometrioma surgery videos on YouTube were useful, although view ratio was high. In a study by Lee et al. (22), half of the hysterectomy videos on YouTube were found to be of low quality. In the literature, there is only one study evaluating uterine fibroids and myomectomy related videos shared online (23). This study found that the quality of YouTube videos, especially those not shared by health professionals, was low. In another study aimed at assessing the reliability and quality of YouTube videos discussing ovarian cysts, researchers identified 50 relevant videos and evaluated them using the discern score and GQS (24). The videos were divided into three categories based on scores: misleading/poor quality (54%), medium quality (18%), and useful/good quality (28%). Overall, the study highlights that YouTube videos related to ovarian cysts tend to be of low quality. Notably, videos produced by non-medical professionals attracted more attention despite their lower quality compared to those created by medical professionals. In the present study, at least half of YouTube videos were evaluated as low quality, regardless of the thresholds used in LAP-VEGaS video assessment tool. Therefore, it may be suggested that YouTube videos are still not sufficient in terms of surgical content. The lack of peer review process may lead to this situation amongst videos on YouTube.

WebSurg is a professional video sharing platform from IRCAD and allows surgery-related content produced by professionals to be shared with healthcare providers. It is reasonable to assume that WebSurg would have more accurate contents than YouTube. In a study by Anand et al. (25), all thoracoscopic lobectomy videos on WebSurg had high quality, however only three of ten of the most-viewed videos on YouTube had sufficient quality. In another study by Yuksel and Çulcu (8), laparoscopic gastrectomy videos on WebSurg were evaluated as superior to videos on YouTube. In the first WebSurg and YouTube comparison made in the field of gynecology, treatment score of US and position of patient, standardized step by step fashion, intraoperative findings, commentary and total scores of LAP-VEGaS were found to be better for laparoscopic hysterectomy videos on WebSurg (7). Similarly, the present study revealed that WebSurg was superior to YouTube, in terms of both total score and proportion of good quality videos when assessed by the LAP-VEGaS video assessment tool. In contrast, some studies have shown that YouTube was as good as WebSurg (9).

In a study, the goal was to compare the quality, educational value, and source accuracy of laparoscopic adrenalectomy videos on two online platforms. The researchers selected the most viewed videos from YouTube using the keyword "laparoscopic adrenalectomy." Novel scoring systems were employed to assess data quality, educational value, source accuracy, and technical quality. The study concluded that while WebSurg videos, often provided by academicians and subject to professional review, fell short of expected quality, selectively chosen YouTube content on laparoscopic adrenalectomy was nearly as accurate as the WebSurg content. However in this study, an unvalidated scale was used to evaluate the videos on both platforms. In the present study, the videos were evaluated with commonly used tools: US, GQS, mDS and LAP-VEGaS video assessment tool. These scales were carefully selected to address this limitation. US, GQS, and mDS are commonly used scales in the literature (11,26-29) while LAP-VEGaS, is not only more comprehensive than the others tools but has also undergone a validation study (14). In the present study the LAP-VEGaS video assessment tool was probably more successful in detecting the difference between the groups of videos than other simple scoring systems, probably due to its detailed questions. Therefore, it can be suggested that appropriate and validated scales should be used to determine the difference between videos hosted on the two platforms.

Study limitations

There are some strengths and limitations in our study. This is the first study to compare laparoscopic myomectomy videos on the WebSurg and YouTube platforms. This is the main strength, as it addresses a novel question and contributes to the understanding of video content across these two major educational platforms. The use of four distinct scoring systems, which are commonly used and/or validated, further enhanced the objectivity and comprehensiveness of our assessment process.

However, as with any study, there are certain limitations that warrant consideration. Firstly, the limitation in the availability of laparoscopic myomectomy videos on the WebSurg platform posed a challenge in terms of sample size. This situation could potentially influence the diversity and representation of videos in our analysis, impacting the generalizability of our findings. Additionally, the undisclosed algorithm behind the "most relevant" filter employed by YouTube for video retrieval introduces an element of uncertainty. This opacity in the search mechanism might have inadvertently influenced the selection and inclusion of videos in our study, introducing an inherent bias that we acknowledge.

Conclusion

We found that WebSurg was superior to YouTube in terms of quality of laparoscopic myomectomy videos. This may have been due to the peer review process applied to videos on WebSurg. Creating a medical sub-category, supervised by health professionals, on YouTube may improve the quality and utility of medical content sharing on this extremely popular platform.

Ethics Committee Approval: *As we used publicly-available data, the ethical approval was not needed.*

Informed Consent: *As we used publicly-available data, the informed consents was not needed.*

Author Contributions: *Concept: S.C., F.A.; Design: S.C., F.A.; Data Collection or Processing: S.C., F.A.; Analysis or Interpretation: F.A.; Literature Search: S.C., F.A.; Writing: S.C., F.A.*

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Combined delta neutrophil index and red blood cell distribution width as a new biomarker to predict endometriosis

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Abstract

Objective: The aim of this study was to evaluate the use of delta neutrophil index (DNI) in predicting endometriosis.

Material and Methods: A retrospective, case-control study was performed in a tertiary care center. DNI, red cell distribution width (RDW), and other blood parameters obtained from complete blood counts of 267 patients, consisting of 122 (45.7%) endometriosis patients with proven pathology reports of stages 3-4, and a control group of 145 women who underwent laparoscopy for simple ovarian cyst and/or diagnostic purposes and had normal histopathology, were compared. Receiver operating characteristic and logistic regression analyses were performed.

Results: DNI and RDW were significantly higher in endometriosis patients than in the control group ($p=0.034$ and $p=0.003$, respectively). Other parameters obtained from complete blood counts (leukocyte, neutrophil, lymphocyte, monocytes, and platelet counts and neutrophil-to-lymphocyte ratio), did not differ ($p>0.05$). For DNI, at a cut-off value of 0.025, area under the curve (AUC) was 0.572 and it was statistically significant [$p=0.042$; 95% confidence interval (CI): 0.503-0.642, sensitivity: 45.9%, specificity: 67.6%, Youden's index: 0.135]. For RDW, AUC: 0.601 for cut-off value of 13.65 was statistically significant ($p=0.004$, 95% CI: 0.553-0.669, sensitivity: 50.8%, specificity: 67.6%, Youden's index: 0.184). The logistic regression model established with the combined marker obtained by multiplying the DNI and RDW was statistically significant ($p<0.001$, Nagelkerke $R^2=0.72$, 95% CI: 2.58-47.26, B: 2.40, negative predictive value: 78.6%, positive predictive value: 37.7%).

Conclusion: DNI, a new inflammatory marker, and RDW, known to be associated with inflammation, may be useful minimally invasive biomarkers of endometriosis. (J Turk Ger Gynecol Assoc 2024; 25: 30-7)

Keywords: Endometriosis, delta neutrophil index, red blood cell distribution width, inflammation, biomarker

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Introduction

Endometriosis is an estrogen-dependent disease, defined as the implantation and growth of endometrial cells outside the uterine cavity and it affects approximately 10% of young women of reproductive age (1). It is a challenging disease for both patients and physicians as it is difficult to diagnose and treat and causes a decreased quality of life. Although dysmenorrhea and dyspareunia are the most common symptoms, endometriosis may also cause bladder and/or intestinal pathologies. Clinical diagnosis is difficult as these symptoms are not specific to endometriosis. Even though imaging techniques, such as ultrasonography and magnetic resonance imaging, are beneficial, especially in the diagnosis of deep infiltrating endometriosis and ovarian endometrioma (OMA), (2) laparoscopy is still the gold standard approach for definitive diagnosis, which provides the definitive histopathological diagnosis. However, both surgery for endometriosis with deep infiltration into the pelvic organs and visual diagnosis during laparoscopy require significant surgical experience (3).

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Invasive surgical methods do not help in minimal and mild endometriosis (4). In addition, since it is an invasive procedure, most patients do not want to have surgery, and this causes a delay in diagnosis of up to eight years (5). Although the most commonly used biomarker for the preoperative diagnosis of endometriosis is the tumor marker, cancer antigen-125 (CA-125), which is synthesized by the coelomic epithelium, it is not specific for endometriosis and has low sensitivity and specificity for the diagnosis of endometriosis compared to laparoscopy (6). Thus, identifying a biomarker that would be more specific in the preoperative diagnosis of endometriosis and OMA has become a target for better management of endometriosis and an ongoing research topic (6).

In endometriosis, the suggestion that cytokines play a role in the ectopic implantation of endometrial cells (7), the high levels of proinflammatory cytokines reported in pelvic fluids of women with endometriosis compared to controls, changes in circulating white blood cell counts, increased serum proteins such as C-reactive protein (CRP) (8), and the demonstration of neutrophilia and lymphocytopenia are evidence to support the view that endometriosis is a local inflammatory disease with systemic subclinical manifestations (8). Inflammation in endometriosis is associated with immune clearance, modification of endometrial cell proliferation, prevention of invasion, and angiogenesis (9). Subsequent studies of the mechanism of inflammation in endometriosis patients focused on inflammatory cells, and endometriosis has been reported to be a risk factor for developing the severe pelvic inflammatory disease (10).

Delta neutrophil index (DNI) is defined as a measure of the immature granulocyte (IG) fraction, which reflects the ratio of circulating IG to the total neutrophil count and can be detected by modern automatic hematology analyzers (11). The term IG encompasses the cell types myelocytes, promyelocytes, and metamyelocytes that are all neutrophil precursors found in the bone marrow after the neonatal period. It has been shown that these immature neutrophil forms enter the circulation during infection (11). In recent years, it has been suggested that DNI is predictive and prognostic in infectious conditions, such as acute appendicitis, bacterial peritonitis, and sepsis (11-13). Although red cell distribution width (RDW) was a biomarker originally associated with anemia, it has recently been accepted as a marker related to inflammation (14). Inflammation disrupts iron metabolism, shortens the lifespan of erythrocytes, and the erythropoietin response causes an increase in measures of RDW (15).

Even though increased inflammatory response in patients with endometriosis has previously been evaluated for various biomarkers, the relationship between DNI, a new inflammatory marker, and endometriosis has not been studied. The aim of the present study was to investigate the use of DNI, which can be determined easily with complete blood count parameters, in diagnosing stage 3-4 endometriosis, which still does not have an ideal and reliable marker and unfortunately requires invasive procedures such as laparoscopy.

Material and Methods

The presented retrospective, clinical study was performed between September 2019 and March 2022 at a university hospital, in the department of obstetrics and gynecology. The study was approved by the Afyonkarahisar University of Health Sciences Clinical Research Ethics Committee Medical Ethics Committee (approval number: 2022/507). Informed consent was obtained.

Patients' medical records were reviewed retrospectively, and clinical, demographic, laboratory and surgical data were obtained. The patient group consisted of endometriosis patients who were operated on for endometriosis and/or endometrioma and who had endometriosis proven by histopathological examination. The control group was formed of age-matched patients who underwent laparoscopy or laparotomy due to unexplained infertility, chronic pelvic pain, bilateral tubal ligation, and simple ovarian cyst, who had no macroscopic endometriotic lesions, no history of endometriosis, and normal findings on subsequent pathology evaluation. All patients were caucasian, non-pregnant women, aged 18-45 years. Patients with systemic and infectious-inflammatory diseases, endocrine disorders, autoimmune diseases, tuberculosis, malignant disease, menopause, obesity, hepatic and renal diseases, and hematopoietic system diseases were excluded. The histopathological diagnoses of all patients and blood analyses obtained during preparation for the operation were recorded. Complete blood counts were performed on a Sysmex XE-2100 hematology analyzer (Sysmex, Kobe, Japan) and CA-125 levels were measured by electrochemiluminescence immunoassay (Cobas 8000 e602).

For this study, the primary outcome was whether there was a difference in DNI between the endometriosis and control groups, and the secondary outcome was to investigate the predictive value of DNI for endometriosis.

Statistical analysis

The distribution of continuous variables is presented as mean and standard deviation (SD) values, while categorical variables are given as ratios and percentages of the total. Comparison of continuous variables between groups was performed with Student's t-test or Mann-Whitney U test, depending on the normality of the distribution. Receiver operating characteristic (ROC) analysis determined the appropriate cut-off point for

individual indicators and was used to calculate sensitivity and specificity. The optimal significant cut-off value was calculated by Youden's index. LR was determined as sensitivity/(1-specificity). Logistic regression analysis was used to predict the effect of the combined biomarker on endometriosis, which was calculated by multiplying the RDW level with the DNI at a 95% confidence interval (CI).

Results

A total of 353 patient records were reviewed. Excluded patients were: 41 with missing complete blood count parameters; 38 older than 45 years of age; two younger than 18 years of age; two with menopause, and three with pelvic inflammatory disease. The resulting study population (n=267) consisted of 122 patients diagnosed histopathologically with endometriosis and 145 controls without endometriosis determined during surgery and/or by histopathological evaluation. The patients in the endometriosis group were patients with deep pelvic endometriosis, tubal diffuse endometriosis, and stage 3-4 (moderate-severe) endometriosis due to OMA (16). No patient findings suggested mild endometriosis in the patient records. There was no difference in mean age between the two groups; mean ± SD age in the endometriosis group was 34.84±6.75 years and in the controls was 34.09±6.94 years (p=0.379). DNI, RDW and CA-125 were significantly different in the endometriosis group compared to controls; DNI was 0.0278±0.0197 vs. 0.220±0.0092 (p=0.034), RDW was 14.443±2.515 vs. 13.594±2.0164 (p=0.003) and CA-125 was 82.19±178.51 vs. 25.81±35.62 (p<0.001) in the endometriosis and control groups, respectively. No differences were observed between the two groups among the other complete blood count parameters [leukocyte, neutrophil, lymphocyte, monocyte, and platelet counts, and the neutrophil-to-lymphocyte ratio (NLR)] (p>0.05) (Table 1). DNI, RDW, and CA-125 were all significantly positively correlated with the diagnosis of endometriosis (p<0.05 for all; r=0.13, r=0.19 and r=0.44, for DNI, RDW and CA-125, respectively). In ROC analysis, for DNI, the cut-off value was 0.025 and AUC was 0.572, being statistically significant (p=0.042; 95% CI: 0.503-0.642, sensitivity: 45.9%, specificity: 67.6%, Youden's index: 0.135). For RDW, the cut-off value was 13.65 and AUC was 0.601 (p=0.004, 95% CI: 0.553-0.669, sensitivity: 50.8%, specificity: 67.6%, Youden's index: 0.184). In the patient records, the number of patients whose CA-125 value was available was 141 consisting of endometriosis (n=85) and controls (n=56). As previously reported, CA-125 was significantly higher in the endometriosis group (p<0.05) (6). When ROC analysis was performed for CA-125, for a cut-off value of 28.54, AUC was 0.759 (p<0.001). In ROC analysis the specificity of the combination of DNI and RDW was close to that for CA-125 alone (78.6% vs. 76%) (Figure 1) (Table 2). For CA-125, although the AUC value was higher than both RDW and DNI, the number of patients for whom we could reach CA-125 was much less (n=267 vs. 141). The combined marker obtained by multiplying DNI and RDW significantly predicted the diagnosis of endometriosis (p<0.001, Nagelkerke R^2=0.72, 95% CI: 2.58-47.26, B: 2.40, negative predictive value: 78.6%, positive predictive value: 37.7%) (Table 3). The significant cut-off value for the combined marker was 0.38 (p=0.003; AUC: 0.606; 95% CI: 0.537-0.674; Youden's index: 0.20; sensitivity: 44.3%; specificity: 76%) (Figure 2).

Table 1. The comparison of inflammatory markers and baseline characteristics between endometriosis and control groups

	Endometriosis patients, (n=122)	Control group, (n=145)	p
DNI (IG: µL)	0.0278±0.0197	0.0220±0.0092	0.034[a]
RDW	14.443±2.515	13.594±2.0164	0.003[b]
Combined DNI/RDW	0.41±0.32	0.23±0.14	0.003[a]
CA-125 (IU/mL)	82.19±178.51	25.81±35.62	<0.001[a]
NLR	3.58±4.042	2.84±1.75	0.634[a]
WBC (10^3/µL)	7.77±2.018	7.77±1.976	0.997[b]
Lymphocytes (10^3/µL)	1.98±0.68	2.02±0.63	0.612[b]
Neutrophils (10^3/µL)	5.05±2.19	5.06±1.78	0.553[a]
Platelets (10^3/µL)	268.71±66.17	265.92±69.13	0.737[b]
MPV (fL)	10.57±0.96	10.49±0.98	0.461[b]
Age (years)	34.84±6.75	34.09±6.94	0.379[a]
Having a child (%)	47.6	41.5	0.347[c]
Irregular menstruation (%)	56.7	43.3	0.169[c]

[a]Mann-Whitney U test. [b]Student's t-test. [c]Pearson chi-square, DNI: Delta neutrophil index, IG: Immature granulocyte, RDW: Red blood cell distribution width, CA-125: Cancer antigen-125, NLR: Neutrophil-to-lymphocyte ratio, WBC: White blood cell count, MPV: Mean platelet volume

Discussion

In the present study, the combination of two biomarkers (DNI and RDW) had a better AUC (0.606) performance for moderate-to-severe endometriosis and a better specificity (76%) than either of the biomarkers in isolation (both 68%). However, CA-125 alone had a larger AUC (0.760) and better sensitivity (65%), but its specificity was similar to that of the combined marker (79%). In previous studies CA-125 has been reported to have low sensitivity for the diagnosis of endometriosis (6). Furthermore, CA-125 levels fluctuate according to the menstrual cycle phase (17). Kitawaki et al. (18) demonstrated that CA-125 level was below 20 IU/mL in 10.6% of OMA patients and 15.6% of middle-stage endometriosis patients. Thus, CA-125 alone does not appear to be sufficient as a marker for endometriosis. We believe that a combination of DNI with RDW may serve as an additional useful biomarker for moderate to severe endometriosis, especially when CA-125 assays are unavailable or unreliable. To date, no single marker with high sensitivity and specificity has been identified for endometriosis. Instead, it has been suggested that a combination of markers may more accurately predict endometriosis (6). We found that the combination of DNI with RDW was helpful in identifying endometriosis.

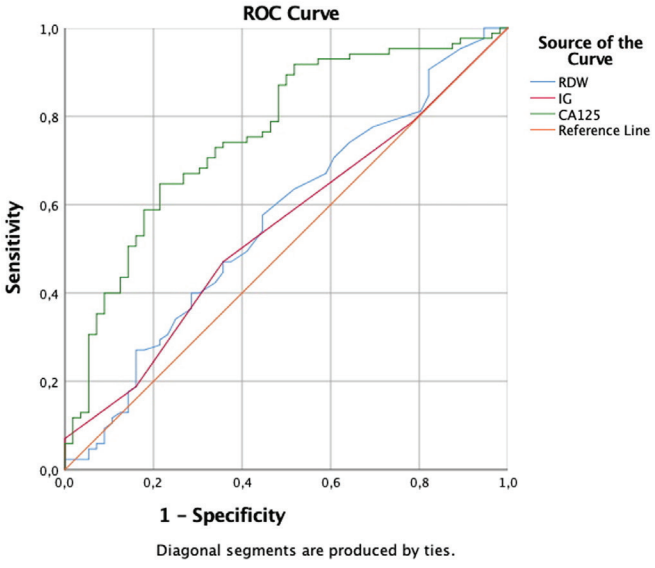

Figure 1. ROC analyses of DNI, RDW, and CA-125 for prediction of stage 3-4 endometriosis
ROC: Receiver operating characteristic, DNI: Delta neutrophil index, RDW: Red blood cell distribution width, CA-125: Cancer antigen-125, IG: Immature granulocyte

Although the sensitivity and specificity of DNI were poor, the result was significant for a cut-off value of 0.025 (AUC: 0.572; p=0.042). The cut-off value for RDW of 13.65 performed somewhat better (AUC: 0.601; p=0.004). The fact that both markers are obtained very simply from complete blood count data on modern hematology autoanalyzers is an advantage. In the present study, all patients were stage 3-4 endometriosis due to either OMA and/or widespread pelvic-peritoneal-tubal endometriosis in the patients who received surgical treatment (16). There are three clinical forms of the disease: superficial peritoneal endometriosis; deep infiltrating endometriosis; and OMA (19). However, their histopathological and immunohistochemical features are similar (20). Although there were no mild endometriosis patients in the present

Table 2. Comparison of the ROC analyses of four markers (DNI, RDW, combination of DNI and RDW, CA-125) for diagnosis of stage 3-4 endometriosis

Markers	AUC	Sensitivity, (%)	Specificity, (%)	Cut-off	(95% CI)		Youdan's index	p
					Lower limit	Upper limit		
DNI	0.572	45.9	67.6	0.025	0.503	0.642	0.13	0.042
RDW	0.601	50.8	67.6	13.65	0.553	0.669	0.18	0.004
DNI and RDW	0.606	44.3	76.0	0.38	0.537	0.674	0.20	0.003
CA-125	0.760	64.7	78.6	28.54	0.678	0.841	0.43	<0.001

P<0.05 is significant. ROC: Receiver operating characteristic, DNI: Delta neutrophil index, RDW: Red blood cell distribution width, CA-125: Cancer antigen-125, AUC: Area under the curve, CI: Confidence interval

Table 3. Logistic regression analysis showing the predictive effect of combined markers on endometriosis (omnibus tests of model coefficients: p=0.001; Nagelkerke R^2: 0.72)

Variables	B	OR	95% CI		Sensitivity, (%)	Specificity, (%)	PPV, (%)	NPV, (%)	p
			Lower	Upper					
Combined marker	2.4	11.04	2.58	47.26	44.3	76	37.7	78.6	0.001

OR: Odds ratio, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value for combined marker (delta neutrophil index and red blood cell distribution width)

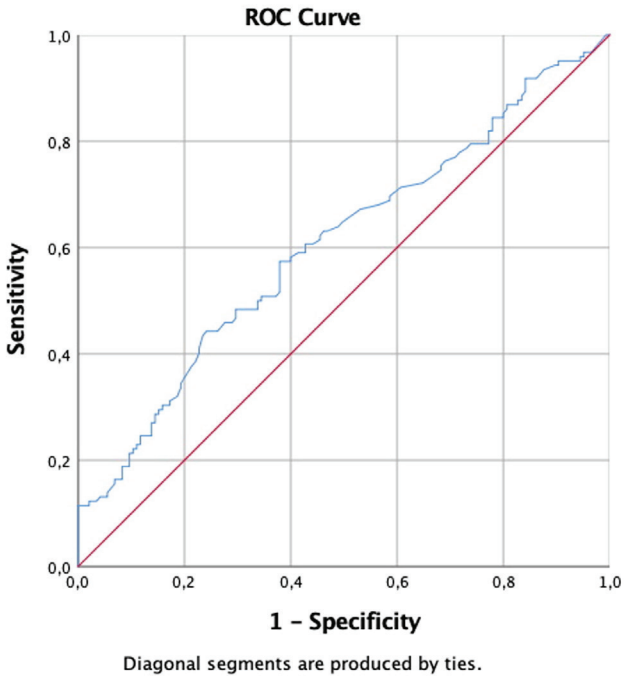

Figure 2. ROC analyses of the combination of DNI and RDW for prediction of stage 3-4 endometriosis
ROC: Receiver operating characteristic, DNI: Delta neutrophil index, RDW: Red blood cell distribution width

study, this situation suggests that DNI and RDW would be useful for predicting endometriosis at all stages due to similar pathogenesis. The insidious, chronic and progressive nature of endometriosis causes a delay of up to 8 years in diagnosing and treating the disease (5). Patients with severe dysmenorrhea may have small lesions in the pelvic cavity, while other patients with moderate to severe endometriosis may be asymptomatic. In addition, diagnostic laparoscopy does not eliminate all possible complications (21). Undiagnosed endometriosis may lead to the risk of infertility in young patients in the following years (22). The gold standard for the definitive diagnosis of advanced endometriosis is laparoscopy. However, laparoscopy in the early stage may be insufficient for diagnosis (4). In addition, for OMA, although imaging methods are helpful (2), there is too much variation in the number of organized blood products within the endometrioma and in the measurement of OMA diameter, which complicates the differential diagnosis of the cystic structure (23). Therefore, the combination of these complete blood count parameters may offer additional diagnostic information for the diagnosis of endometriosis. Combined DNI/RDW may have better sensitivity at all stages and locations of the disease, although this remains to be investigated, and is unaffected by the time of collection, unlike CA-125.

The NLR is the most commonly studied inflammation marker among complete blood count parameters. Jing et al. (24) reported on 662 patients with endometriosis and 83 patients with pathologically benign ovarian tumors, and found that lymphocyte count, CA-125, and NLR were significantly elevated in endometriosis patients. For distinguishing endometriosis from other benign ovarian tumors, the combination of NLR and CA-125 (81.3%) showed greater sensitivity than CA-125 alone (80.6%) (24). The sensitivity of NLR alone (32.9%) in this study was lower than the sensitivity (46%) for DNI in our study. Kim et al. (25) reported that the severity of endometriosis was not associated with either NLR or CA-125 levels. Our results were consistent with these earlier reports. Therefore, NLR does not appear to be an ideal marker. Since peritoneal markers vary greatly according to hormonal effect and amount of peritoneal fluid and are more invasive, serum/blood markers may be more useful in measuring or monitoring disease activity. Furthermore, although a large number of blood-borne molecules have been investigated in research studies, including a wide variety of cytokines, hormones, growth factors, adhesion molecules, and antibody levels (6), the analysis of these molecules may be challenging in routine clinical practice. However, the combination of DNI and RDW, are automatically calculated by modern automated blood analyzers.

Neutrophils play a role in innate anti-microbial and anti-viral immunity but have demonstrated additional function in various tissues under pathological conditions (26). There is growing evidence that neutrophils have a role in endometriosis (27). Systemic inflammation leads to the destruction of circulating mature neutrophils and the loss of active neutrophils. To compensate for this, the number of immature neutrophils in the circulation increases and a left shift occurs where the immature/total granulocyte ratio increases, which is an indicator of sepsis and inflammation (28). Therefore, DNI has been studied as a marker for many inflammatory and infectious diseases. Besides being reported as a diagnostic tool that better predicts mortality during sepsis than CRP (29), it has been indicated to predict perforation in patients with appendicitis (30). DNI has also been studied in obstetric patients. In women with severe preeclampsia, serum DNI value was increased compared to women with normal pregnancy or mild preeclampsia (31). In another study, DNI was a predictive marker for histological chorioamnionitis in patients with preterm premature rupture of membranes (32). In other studies, a higher DNI has been reported as a prognostic marker of conditions such as cardiac arrest and pulmonary embolism, and based on these studies, DNI values were considered to reflect both the severity of the infection and the severity of diseases associated with systemic and sterile inflammation in the absence of infection (33,34). Moreover, DNI is time and cost-effective, as it is simply analyzed with a complete blood count (35). The present study found DNI to be significantly higher in endometriosis patients since

it is known that endometriosis is associated with inflammatory response, and DNI increases inflammation.

In the present study, RDW was significantly larger in the endometriosis group compared to the control group, and its specificity was the same as DNI in predicting endometriosis ($p<0.05$, 68%). Recently, RDW has been recognized as an inflammation-related marker. Inflammation is also a key feature of endothelial dysfunction, and this results in an increased RDW, indicating abnormal erythrocyte survival (14). Besides the disruption of iron metabolism during inflammation and the effect of cytokines released during inflammation, the disruption of the erythropoietin response, leads to anisocytosis and an abnormal RDW. Some evidence indicates the potential role of iron metabolism disorders in the pathogenesis of endometriosis. Iron accumulated in the peritoneal cavity of women with endometriosis causes free radical production, inflammation, and cell damage (36). As a result of all this, it is plausible that RDW is altered in endometriosis, an inflammatory condition (37). In addition, Lippi et al. (38) demonstrated that RDW significantly correlated with CRP and erythrocyte sedimentation rate. In a study consisting of 98 patients, RDW was significantly higher in the endometriosis (n=50) group compared to the control group (n=48), and RDW was found to be associated with the severity of endometriosis (39). In the present study, RDW was significantly wider in the endometriosis group, and our cohort size was larger. Qin et al. (40) determined a positive correlation between endometriosis score and RDW; however, surprisingly, there was no significant association between CA-125 and NLR. As the study population included only women with moderate to severe endometriosis, as in our study, they could not exclude the possibility that NLR was associated with the severity of early-stage endometriosis. However, NLR was not a good marker for assessing the severity of endometriosis in patients with moderate to severe endometriosis (40). In another study, a comparison between patients with stage 3 (n=96) and stage 4 (n=87) endometriosis showed that mean levels of CA-125 and RDW were significantly higher in stage 4 patients than in stage 3 patients (41).

Although OMA is a condition in which advanced endometriosis can be diagnosed preoperatively, many patients with advanced endometriosis may be asymptomatic. It has been suggested that in patients with stage 3 or 4 endometriosis, removing only the OMA and leaving possible pelvic and intestinal endometriotic foci in place would be inadequate treatment (42). In this context, a biomarker that will enable the preoperative identification of stage 3/4 endometriosis patients can provide additional early information when considering extensive pelvic surgery in advance.

Study limitations

This study had some limitations. First, the data used were obtained from a single center, and since it was a retrospective study, causality cannot be determined. DNI was calculated for each patient from a one-off blood sample only. Therefore, we did not know the changes over time. In our clinic, automatic IG count parameters could only be obtained after 2018, which limited the available data and the number of patients. We could not include the patients' body mass indexes since they were not recorded in the patient files. Finally, all patients had been diagnosed with moderate-to-advanced endometriosis and so the combination of DNI and RDW should be assessed in patients with lower grades of endometriosis.

Conclusion

Inflammation-mediated mechanisms play a critical role in the etiology of endometriosis. Therefore, DNI, which is prognostic in many inflammatory and systemic diseases, can be used as a new low-cost and rapid marker in endometriosis. Elucidating how and why DNI is associated with the endometriosis may provide increased understanding of pathophysiology. In this sense, well-designed prospective studies are needed better to understand the role of DNI.

Ethics Committee Approval: *The study was approved by the Afyonkarahisar University of Health Sciences Clinical Research Ethics Committee Medical Ethics Committee (approval number: 2022/507).*

Informed Consent: *It was obtained.*

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

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Importance of hemogram parameters for predicting uterine scar dehiscence

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Abstract

Objective: The pathophysiology of uterine scar dehiscence is not yet clear. The aim of this study was to investigate whether preoperative hemogram parameters can be used as predictive markers of uterine scar dehiscence, thus improving prediction and contributing to management of repeat Cesarean section.

Material and Methods: Between 2015 and 2020, 36670 (47.6%) cesarean sections were delivered in our hospital and 16943 of them had a previous Cesarean section. All cases of uterine scar rupture detected during Cesarean section were identified, and a total of 40 patients were included after excluding cases with impairment of the systemic inflammatory response (SIR). Controls consisted of 40 randomly selected, age- and body mass index (BMI)-matched patients, and the groups were compared.

Results: Age, BMI, and gravidity were similar ($p>0.05$). Although the gestational week and Apgar scores were similar between the groups ($p>0.05$), the birth weight amongst controls was significantly higher than the uterine dehiscence group ($p=0.028$). Platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, and other hemogram values were similar in both groups ($p>0.05$). Mean platelet volume (MPV) in the control group was significantly higher than in the uterine rupture group ($p=0.049$). Regression analysis found no significant result between hemogram parameters, birth weight, and dehiscence.

Conclusion: In this study, which set out to identify predictors of the risk of uterine scar dehiscence with SIR parameters, only the MPV value was lower in the dehiscence group. (J Turk Ger Gynecol Assoc 2024; 25: 38-43)

Keywords: Uterine scar dehiscence, Cesarean scar, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, mean platelet volume

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Introduction

Uterine rupture can cause adverse consequences for mother and fetus. Uterine rupture is divided into two main types; incomplete uterine rupture or dehiscence refers to the incomplete separation of uterine scar tissue with an intact serosal layer while complete uterine rupture is a catastrophic event where a full-thickness disruption of a scar occurs, especially during labor, responsible for maternal-fetal morbidity and mortality (1). Uterine scar dehiscence can occur during late pregnancy or active labor and, rarely, in the postpartum period. Following any conditions in the pre-pregnancy period, such as myomectomy, Cesarean section, hysterotomy and curettage, that disrupt the integrity of the uterus, uterine scar dehiscence may occur and rupture during the perinatal period. Factors that increase uterine tension, such as fetal macrosomia, polyhydramnios, and multiple pregnancies, increase the risk of uterine rupture and dehiscence (2,3). The pathophysiology of uterine scar dehiscence has not yet fully understood. It is thought that previous uterine infection and/or inflammation can lead to scar tissue weakness, and eventually scar dehiscence occurs (3).

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Previous Cesarean section is a significant independent risk factor for uterine rupture associated with adverse maternal and perinatal outcomes (4). A systematic review showed an average incidence of 0.05% uterine rupture in all pregnancies and 1% in women who had a previous cesarean delivery (5). However, the true incidence of uterine dehiscence is not fully known. In some studies, the reported incidence rates varied from 0.06% up to 3.8% and were predicted to increase in association with the rising cesarean rates (6-8).

White blood cell count (WBC) has been widely used as an inflammatory biomarker in clinical practice for years. Moreover, peripheral blood neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are simple systemic inflammatory response (SIR) parameters that can be easily acquired by a simple complete blood count (CBC) test. They are calculated by dividing the neutrophil or platelet count by the lymphocyte count (9). Many studies have been done on the predictive values of these parameters for preeclampsia, tubal ovarian abscess, diabetes mellitus, coronary artery disease, ulcerative colitis, and inflammatory arthritis (10-12). It has been suggested that platelets also play important roles in immune and/or inflammatory processes (12,13). Mean platelet volume (MPV), a measure of platelet size and a good indicator of platelet activation and function, is increasingly becoming a useful marker of inflammation (14-16).

The aim of this study was to examine whether blood parameters produced during a CBC test that are used as markers of inflammation-infection are associated with the risk of uterine scar dehiscence in cases with repeat Cesarean section and to investigate preoperative hemogram parameters in predicting pregnancies with uterine scar dehiscence. Identifying such biomarkers would improve the identification of women at high risk for rupture and contribute to their management.

Material and Methods

The study was planned as a retrospective, observational study. Among the patients admitted to the Department of Obstetrics and Gynecology of the University of Health Sciences Turkey, Etlik Zübeyde Hanım Women's Health Training and Research Hospital between June 2015 and June 2020 and delivered by Cesarean section, cases with uterine scar dehiscence reported intraoperatively were evaluated.

The Local Ethics Committee of the University of Health Sciences Turkey, Etlik Zübeyde Hanım Women's Health Training and Research Hospital granted its approval for the study's conduct, protocol, and procedures (approval number: 14, date: 14.09.2020). This hospital is a tertiary reference center with around 15,000 births per year. To ensure homogenization, women having multiple repeat Cesarean sections who were at high risk for uterine scar dehiscence were excluded. The patients who had only one previous Cesarean section and cases with a single layer of continuous suture in previous Cesarean section surgery notes were included in the study. Informed consent was obtained from patients who participated in this study. Patients who experienced no complications during their pregnancy and were taken to an elective Cesarean section with a previous cesarean indication were divided into two groups:

Group 1, control group (patients with no uterine scar dehiscence); and group 2, patients with uterine scar dehiscence identified and confirmed during their second cesarean delivery.

After the exclusion criteria were applied, the control group was composed of patients who were age- and body mass index (BMI)-matched and had experienced only one Cesarean section with no scar dehiscence. The randomization was based on the chronological order of the hospital data. The first patients meeting the criteria whose Cesarean section came after each dehiscence patient' were taken for inclusion amongst controls until matching group sizes were achieved.

Exclusion criteria

Patients with multifetal pregnancies and comorbid diseases, women who had no cesarean delivery before and experienced more than one cesarean, and whose gestational age at delivery was less than 37 and greater than 42 weeks were excluded. Both low birth weight (<2500 grams) and fetal macrosomia (>4000 grams) at delivery, patients with amniotic fluid abnormalities, pregnancy complications, such as gestational diabetes mellitus, intrauterine growth restriction, preterm premature rupture of the membranes, gestational hypertension, intrahepatic cholestasis and patients with missing data were not included in the study.

All Cesarean sections of the included patients were performed with a locked, single-layer uterine closure. Patients who received the unlocked double-layer closure technique were also excluded. Although there is no known difference in dehiscence between single-layer and double-layer, in order to avoid heterogeneity and biases in the cohorts, the entire population in this study was formed from cases in which single-layer sutures were applied.

Obstetric history (gravida, parity), ultrasonographic findings (biophysical profile, fetal biometry), comorbid diseases, if any, previous surgical procedures, hemogram parameters (WBC, hemoglobin concentration, NLR, PLR, MPV), postoperative blood loss, blood transfusion requirement, number of postoperative hospitalization days, maternal/fetal mortality rates, and neonatal demographics and outcomes (gestational age at birth, birth weight, Apgar scores, neonatal complications, admission rates and length of stay in neonatal intensive care unit) were reported and compared between two groups.

Statistical analysis

Before the data analyses, all data were checked to detect anomalies and inaccuracies. Normality was tested using the Kolmogorov-Smirnov, skewness-kurtosis values, and histogram. An independent samples t-test to compare the two groups' differences for parametric data for all continuous variables. The uterine scar dehiscence rate was calculated by dividing the number of patients with dehiscence by the number of patients with previous Cesarean sections.

For non-parametric data, the Mann-Whitney U test was used to compare the differences between two groups. Differences between categorical data were assessed using Fisher's exact test and reported as frequencies and percentages. The effects of variables, including NLR, PLR, MPV, hemoglobin concentration, WBC, and MPV values and birth weight on the group were investigated by logistic regression. Data were analyzed using SPSS version 23.0 (IBM Inc., Armonk, NY, USA) and a $p<0.05$ was considered statistically significant.

Results

During the study period 77,081 (100%) deliveries occurred in the hospital. Of these, 40,407 (52.4%) were vaginal births, the remaining 36,674 (47.6%) were Cesarean sections, and 16,943 of the Cesarean sections had a previous Cesarean section history (Figure 1). There was a total of 157 uterine scar dehiscences and 40 (25.5%) cases were included in the study group after exclusions. Forty randomly selected controls were also selected. Further, the incidence of uterine scar dehiscence by years is presented in Table 1. From 2015 to 2020, the incidence of uterine dehiscence ranged from 0.26% to 0.55%.

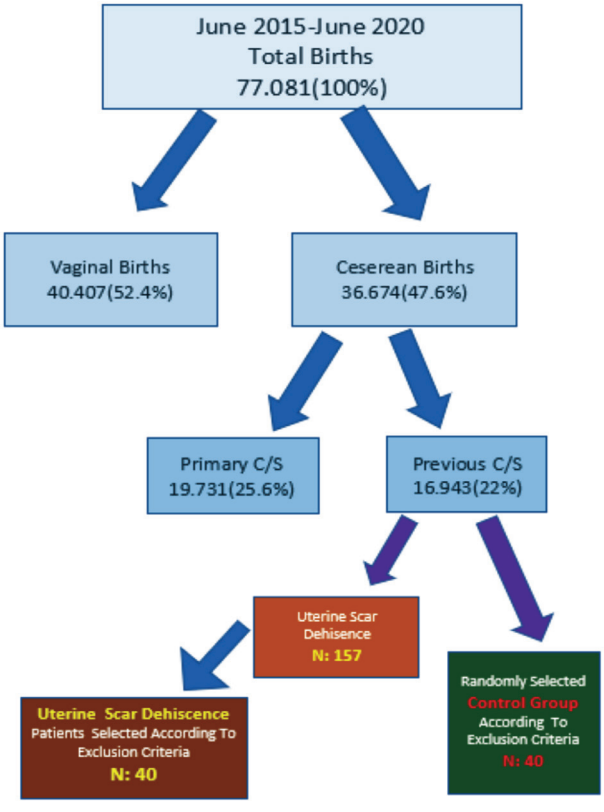

Figure 1. Flow chart of this study

The results of the comparison between the cases with dehisence and the controls are shown in Table 2. The study design ensured that age, BMI, and gravidity values were similar ($p>0.05$). In addition to the gestational week, 1st and 5th-minute Apgar scores, and fetal presentation were also similar between the groups ($p>0.05$). However, the birth weight of babies born in the control group (3397.63±418.15 g) was significantly higher than the uterine dehiscence group (3176.25±462.54 g) ($p=0.028$). SIR parameters such as PLR (147.79±54.72% vs. 132.99±61.24%) and NLR (4.14±1.39% vs. 4.06±1.38%) were similar in both groups ($p>0.05$). Also, there was a similarity between the groups in preoperative and postoperative hemoglobin values and leukocyte counts ($p>0.05$). However, the control group's preoperative MPV level was significantly higher than the uterine dehiscence group ($p=0.049$) (Figure 2). The relationship between the group and the complication and blood transfusion volume (units) could not be conducted because the chi-square analysis assumptions were not met, as seen in Table 3. No complications were detected in 90% of the dehiscence group and 97% of the control group. While two cases in the dehiscence group needed a blood transfusion, transfusion was required in one case in the control group. Postpartum hysterectomy was performed in one patient in the dehiscence group and respiratory arrest occurred in one patient. LR analysis showed variables, including NLR, PLR, MPV, hemoglobin concentration, WBC, and MPV values, and birth weight had no effect ($p>0.05$; Table 4).

Discussion

Maternal and fetal outcomes of uterine rupture can include both morbidity and mortality. The maternal mortality rate was 1/500 in the literature, while the reported perinatal mortality rate associated with uterine rupture ranged from 5% to 26% (17-19).

Table 1. Incidence of cases with uterine scar dehiscence by year

Year of operation	n (%)	Delivery number	Incidence
2015 (last half)	10 (6.4)	8239	0.26
2016	20 (12.7)	16358	0.26
2017	41 (26.1)	16201	0.52
2018	32 (20.4)	15260	0.43
2019	38 (24.2)	13978	0.55
2020 (first half)	16 (10.2)	7045	0.50

Table 2. Comparison of obstetric, demographic and hemogram parameters of the groups

Mean ± SD, median (range) or n (%)		Uterine dehiscence group	Control group	p
Age (years)*		28.43±6.05	29.90±4.19	0.209
BMI (kg/m²)*		28.60±3.83	28.83±3.55	0.786
Gravida**		2 (2-6)	2 (2-6)	0.326
Gestational age (weeks)**		38 (36-39)	39 (34-40)	0.137
Preop Hb (g/dL)*		11.69±1.30	11.75±1.15	0.814
Postop Hb (g/dL)*		10.84±1.21	10.95±1.16	0.677
Preop WBC**		951500 (561000-1964000)	853000 (421000-1721000)	0.071
Preop NLR*		4.14±1.39	4.06±1.38	0.802
Preop PLR*		147.79±54.72	132.99±61.24	0.258
Preop MPV*		8.73±0.80	9.13±0.99	**0.049**
Birth weight (grams)*		3176.25±462.54	3397.63±418.15	**0.028**
Apgar 1 min**		9 (7-9)	9 (9-9)	0.155
Apgar 5 min**		10 (9-10)	10 (10-10)	0.155
Presentation***	Vertex	39 (97.5)	39 (97.5)	0.753
	Breech	1 (2.5)	1 (2.5)	

*Independent sample t-test, **Mann-Whitney U test, ***Fisher's exact test, BMI: Body mass index, Hb: Hemoglobin, WBC: White blood cells, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MPV: Mean platelet volume, SD: Standard deviation, min.: Minute

Table 3. Complication and transfusion rates of the groups

	Uterine dehiscence group, n (%)	Control group, n (%)
Complication		
None	36 (90.0)	39 (97.5)
Maternal blood transfusion	2 (5.0)	1 (2.5)
Respiratory arrest	1 (2.5)	0 (0.0)
Postpartum hysterectomy	1 (2.5)	0 (0.0)
Blood transfusion volume (units)		
None	38 (95)	39 (97.5)
2	1 (2.5)	1 (2.5)
3	1 (2.5)	0 (0.0)

Table 4. Binary logistic regression analysis

Independent variables	p	OR	95% CI for exp (B)	
			Baseline	Saturated
EFW	0.886	1.000	1.000	1.000
NLR	0.936	1.004	0.907	1.111
PLR	0.664	1.001	0.998	1.004
MPV	0.841	0.995	0.948	1.045
Hb	0.978	0.999	0.963	1.037
WBC	0.693	1.000	1.000	1.000
Dependent Variables: Control & Uterine Dehiscence Groups				

Hb: Hemoglobin, WBC: White blood cells, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MPV: Mean platelet volume, OR: Odds ratio, CI: Confidence interval

Death is most likely to occur in cases of placental separation and fetal extrusion (20,21).

A challenging decision the surgeon faces in uterine rupture-uterine scar dehiscence is whether the repair of rupture can be facilitated or urgent hysterectomy should be necessary for life-saving measures (21). It should be noted that Vaginal Birth after Cesarean Section has become more popular, particularly in the setting of increased cesarean rates worldwide, leading to an increased risk for maternal, fetal, and neonatal complications. Thus, useful predictive tools are needed to determine if a patient can undergo a trial of labor after cesarean safely. Ultrasonography has been used widely to predict uterine scar rupture. A relationship between the scar thicknesses as measured by sonography and the scar rupture risk was reported in some studies (22,23). Unfortunately, an optimal scar thickness cut-off value specifically designed for predicting increased rupture-dehiscence risk was not established. Therefore, cut-off value and management decisions were left to clinicians.

Studies have shown that maternal infection-inflammation may be associated with uterine scar dehiscence (3). There are many recent studies about NLR and PLR as useful inflammation markers. Some studies were conducted to predict whether these markers were related to pregnancy outcomes, preeclampsia, and fetal loss (24-26). I addition, MPV has been found to be another useful biomarker of inflammation (14). There is no previous study conducted to predict uterine scar dehiscence with these ratios and MPV, to the best of our

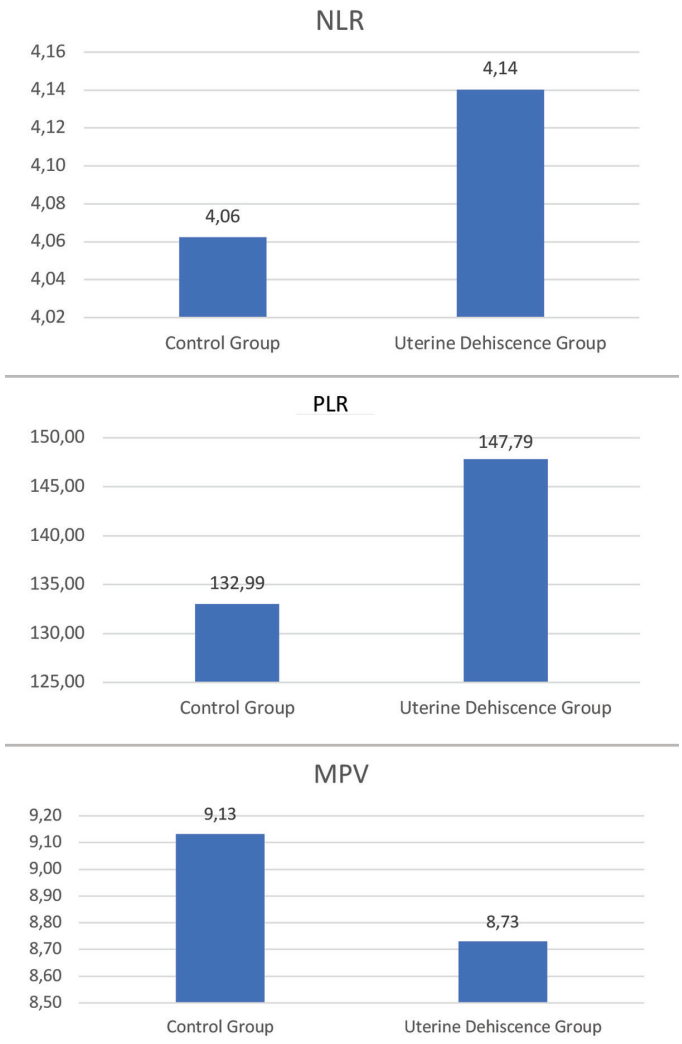

Figure 2. Comparison of NLR, PLR, and MPV levels in control and uterine dehiscence groups

knowledge.

We investigated whether hemogram parameters associated with inflammation can be used as an alternative tool to ultrasonography to predict the increased risk of uterine scar dehiscence. In the present study, we found the difference in MPV values between uterine dehiscence and control groups was significant (p=0.049). However, NLR and PLR values showed no significant difference.

Conclusion

MPV was found to be the only significant predictor of uterine scar dehiscence. Therefore we suggest that MPV may be used to predict uterine scar dehiscence in patients with previous cesarean delivery. Furthermore, a CBC is easy to carry out, easy to evaluate, and affordable compared to other diagnostic tools. We hope our paper will stimulate and guide future larger studies. We are aware that additional, large, well-designed, randomized controlled studies are necessary to confirm our findings.

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Ethics Committee Approval: *The Local Ethics Committee of the University of Health Sciences Turkey, Etlik Zübeyde Hanım Women's Health Training and Research Hospital granted its approval for the study's conduct, protocol, and procedures (approval number: 14, date: 14.09.2020).*

Informed Consent: *Informed consent was obtained from patients who participated in this study.*

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

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Abnormal umbilical cord coiling and association with pregnancy factors

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Abstract

The umbilical cord, as a connecting bridge between two lives, plays an important role in fetal development. Though studies on the umbilical cord date back many years, extensive studies on certain umbilical cord characteristics, such as umbilical cord coiling, are rare. Cord coiling, measured by the umbilical coiling index, is a physiological phenomenon that offers resistance to external pressures. Umbilical cord coiling is a result of several factors, both environmental and genetic. However, umbilical cords sometimes coil abnormally, resulting in hypocoiling, hypercoiling, or non-coiling which have significant associations with adverse perinatal outcomes. An all-language literature search was conducted on Medline from 1970 to 2023. The following search terms were used; umbilical cord; umbilical coiling; coiling index; abnormal coiling; perinatal outcomes, and cross-referencing yielded further information. We comprehensively reviewed the literature on umbilical cord coiling, factors contributing to coiling, abnormal coiling of the umbilical cord, and the association with several factors including maternal age, gravida, gestational diabetes mellitus, pre-eclampsia, abruption, birth weight, intrauterine growth retardation, maternal iron status, small for gestational age, fetal heart rate variations, ponderal index, and sought possible explanations. (J Turk Ger Gynecol Assoc 2024; 25: 44-52)

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Introduction

Normally, the umbilical cord travels from the placenta to the fetal umbilicus, twisting (coiling) as it does so. In 1521, Berengarius noted the umbilical cord vessels' spiral pattern (1). By nine gestational weeks, the umbilical cord's twist, or more correctly, helix, which has been recorded as early as 42 days of gestation, is well-established (2). An umbilical coil is described as one 360° helix of umbilical vessels, which are usually left-oriented (3). Given that the cord's natural tendency to coil implies that there must be a benefit to this from an evolutionary standpoint, the umbilical cord's coiling makes it both flexible and sturdy, and these qualities offer resistance to outside influences that can impair blood flow (4). So abnormal coiling of the umbilical cord has been postulated to be associated with adverse perinatal outcomes. In this review, we aimed to investigate abnormal coiling of the cord and associations of abnormal coiling with various pregnancy factors.

Background

The umbilical cord, also referred to as the navel cord or funiculus umbilicalis, connects the fetus and placenta. By week seven, the umbilical cord is fully formed and replaces the yolk

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sac as the embryo's primary source of nourishment (5). A single umbilical vein and two umbilical arteries are typically seen in the cord, which are enclosed in Wharton's jelly, a supple matrix, rich in proteoglycans (6). This jelly's physical characteristics are comparable to Polyurethane foam, compression- and twist-resistant, and these qualities help in protecting the vital circulatory lifeline that connects the placenta and fetus (7). The placenta delivers nutrient-rich, oxygenated blood to the fetus via the umbilical vein, and umbilical arteries are involved in transportation towards the placenta, thereby allowing the movement of materials to and from without direct mixing. The fetus's health will be seriously compromised if the fetal blood flow through the umbilical cord vessels is compromised (8). The cord is attached to the embryo's ventral surface towards the caudal extremity during the first few weeks of gestation. In the fourth month, the point of attachment is permanently relocated to the centre of the abdomen when the coelom closes and the yolk sac shrinks (9). By six weeks of gestation, an ultrasound can detect the umbilical cord, and by eight to nine weeks, it can be clearly seen. During pregnancy, the umbilical cord is roughly the same length as the fetus's crown-to-rump measurement. At term, the typical length is approximately 50 cm and ranges from 30-100 cm (10).

The arteries and veins of the umbilical cord are distinct from those seen in the rest of the fetus. Internal and external elastic lamina are absent from the walls of the umbilical cord arteries, and mucous connective tissue takes the role of the adventitia that is present in other arteries. An internal elastic lamina, along with a thicker muscularis layer with intertwined smooth muscle fibres make up the umbilical cord vein (11). Doppler velocimetry has been used to examine the blood flow properties of umbilical vessels. The umbilical vein has continuous blood flow, while the umbilical arteries display the distinctive wave pattern which reflects the fetal cardiac cycle (12,13).

Coiling index

Term cords typically have the same number of coils as seen during the first trimester, with the number of coils ranging from 0 to 40, but they can reach as high as 380. This suggests that the cord lengthens by an increase in the pitch between each of its helix turns rather than by an increase in the number of turns (2,14). Four to five per cent of umbilical cords do not coil at all or are poorly coiled (15). After 20 weeks of gestation, 30% of non-coiled cords continue to coil, although a loss of coiling has never been recorded. The fetal side of cords typically exhibits more spiral turns than the placental side (16,17). Coiling can be sinistral (leftward), or dextral (rightward), and occasionally be a mixed pattern, but sinistral is four to eight times more frequent than dextral with no known cause for this leftward bias (4).

In 1954, Edmonds created a system to measure cord coiling. He referred to it as the "Index of twist" since it indicated positive and negative values to the twists based on the direction of coiling (1). This approach was initially simplified by Strong et al. (16) in 1994, through the Umbilical Coiling Index (UCI), which is the ratio of twists to the length of the cord without considering the direction of coiling. However, this method has certain limitations. Every month, the umbilical cord length expands by roughly 3 to 6 cm, with the increase being more pronounced in the second part of pregnancy. As a result, compared to the second trimester, the coiling index is lower in the third trimester. In addition, because various fetuses experience cord lengthening at varying rates, each person's umbilical cord coiling index changes at a different rate. Moreover, different studies have examined the length of the cord in different ways; some studies exclude the segment that is still linked to the newborn (18), while others include all segments of the cord (17). The cord contracts after delivery (19), and so the time between delivery and measurement could affect the UCI and the cord continues to contract following formalin fixation (18). Naturally, the normal mean UCI differs significantly across investigations (20).

The length of the umbilical cord cannot be determined before birth. To measure the coiling index antenatally using ultrasound, a method was developed. This is accomplished by measuring the separation between two neighbouring coils and dividing one by the intercoil distance in centimetres gives the UCI (21). The mean of the UCI was 0.17 coils/cm. The 10^{th} percentile value stood at 0.07 coils/cm and the 90^{th} percentile value was 0.30 coils/cm (22). The UCI is traditionally categorised as hypocoiled/undercoiled (below 10^{th} percentile), normocoiled (10-90^{th} percentile), hypercoiled/overcoiled (above 90^{th} percentile) (23,24).

The management of pregnancy might benefit from prenatal UCI determination. However, a comparative study (25) indicated that if the UCI was derived from a 10 cm segment rather than the entire length of the cord and there was an overestimation of over 25%, thus explaining why the evaluation of prenatal UCI is different from the evaluation of postnatal UCI (24,26). Furthermore, a significant correlation has not been found between UCI determined before delivery using ultrasound and after delivery by examination of the umbilical cord (27).

Patterns of coiling

Four patterns of umbilical coiling are reported, with the "Rope pattern" as the most common pattern, followed by the "Undulating pattern." The other two patterns are "Segmented" and "Linked" (28). A schematic representation of coiling patterns is shown in Figure 1.

Prenatal ultrasonography

Though technological and scientific advances are occurring rapidly in imaging and other fetal evaluation methods, significant constraints are noted in the available screening and diagnostic tests. Sometimes failure to identify fetal distress resulted in unwanted outcomes and other times, increased frequency of intervention for suspected abnormalities is found to be unnecessary. In this search for a reliable tool, antenatal identification of aberrant umbilical cord and umbilical coiling is the research target. Abnormal coiling or absent coiling has long been suggested to be associated with adverse outcomes of pregnancies, and if any are present, it would be important to identify the abnormality prenatally.

The umbilical cord is visible for the majority of the gestation and can be observed shortly after the fetal pole is seen. Due to the difficulty of measuring the umbilical cord with sonography during the first trimester, measurement errors may be significant. Given the reduced amniotic fluid content in the third trimester of pregnancy, it may be challenging to differentiate between umbilical cord coiling and torsion, and measurement errors may also arise (29). Second-trimester measurement is therefore favoured in many studies (30). However, even measurements taken in the second trimester have some disadvantages because it can be too early to detect fetal growth deficiencies (31).

The unbilical cord is divided roughly into three regions; the fetal region, linked to the fetal abdominal wall; the middle region which is free-floating; and the placental region that is attached to the placenta. For each of the three regions of the cord, adequate ultrasonographic visibility rates varied, with all three regions being seen clearly in only around 10% of cases (32). Added to that, attached ends do not accurately reflect cord coiling, while the free-floating segment is the area of the cord that is most susceptible to kinking and compression. Given these limitations, it is preferable to assess the middle region during the second trimester. If the visibility of the cord is adequate, three distinct segments or two to three consecutive segments in the middle region are determined and the mean UCI is calculated (32). However, studies have employed different measurement techniques leading to inter-observer bias, causing comparisons and drawing conclusions unreliable. Generalizing measurement guidelines will reduce inter-observer bias (33).

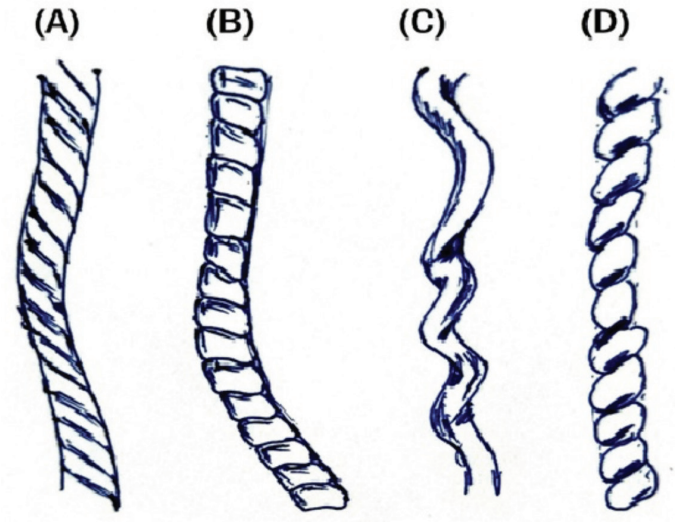

Figure 1. Schematic depiction of umbilical cord coiling patterns. (A) Rope, (B) segmented, (C) undulating, (D) linked

It is standard prctice to examine the umbilical cord's numerous characteristics during a routine second-trimester sonographic examination but the coiling index is not currently recommended (34). There aren't many research studies in this area that support the idea of using UCI for routine screening or even in special cases. Although UCI is indicated as a screening technique for adverse prenatal or antenatal events (35), it is unlikely to be beneficial as a screening tool for deviations from the expected in routine clinical practice, for example in preterm birth, due to its low predictive value (36). After studying 100 uncomplicated singleton pregnancies with no other comorbidities, Ma'ayeh et al. (27) also concluded the same. Mittal et al. (37) noted that UCI has a high negative predictive value for adverse perinatal outcomes. However, all of these studies were conducted with small sample sizes. According to the findings of another investigation, larger studies are necessary to validate the effective predictive ability of unbilical assessment and UCI in predicting the risk of small for gestational age (SGA) (26). Future fetal assessments in high-risk pregnancies may include the ultrasonographic evaluation of the umbilical cord and UCI, depending on the results of larger investigations.

Recently, a machine learning model for classifying images of the fetal umbilical cord using 2-D ultrasound Doppler has gained popularity (38). This development may lead to some progress in this area.

Factors contributing to umbilical coiling

There have been several hypotheses concerning the variables influencing umbilical cord coiling. Some supportive evidence was identified including that coiling patterns do not appear early in the gestation, which is supported by the observation that coiling is absent in early abortion specimens (39).

Some of the hypotheses about factors influencing umbilical coiling proposed in the later half of the 20th century include fetal movements (1), differential growth rates of umbilical vasculature (4), fetal hemodynamic forces (40), and the presence of snarls in the cord (14,32). Regrettably, no further research has focused on these postulates to date. In the

early 21st century, the Roach muscle bundle hypothesis was proposed after conducting microscopic examinations of 251 umbilical cords. The Roach muscle, a small muscle bundle located directly next to the umbilical artery, was discovered in 101 umbilical cords, and the mean UCI was greater in cords with this muscle bundle (23). One interesting study published in 2019 showed that UCI is higher in female newborns compared to males after gestational age, gravidity and parity correction using multiple linear regression analysis (41). Conversely, Qin et al. (32) showed no significant relationship between gender and cord coiling. Once again, both studies had low sample size, and more studies with larger sample sizes must be performed to further investigate these intriguing findings.

There is generally limited evidence available, even concerning factors that are considered not to be associated with umbilical cord coiling. Such studies were on the thickness of the umbilical cord (42), parity and gravida (43), chorionicity, and zygosity (44,45). All these studies concluded no relation between the investigated factors and cord coiling. The age of the mother might be a confounding factor for the studies on parity, chorionicity, and zygosity (46). All these proposals put forward one or two variables, but recent studies show coiling is multifactorial with both environmental and genetic involvement (46).

Umbilical blood vessel flow characteristics and umbilical coiling

When pressures are monitored concurrently, the pulse pressures of the umbilical arteries and umbilical vein are 180° out of phase. During pulsations, arteries lengthen and the diameter narrows, and this mechanism causes the widening of the vein's diameter and experiences a relative drop in pressure. The venous blood is pumped forward in this manner. The greater the number of coils, the greater the impact of the arteries' pressure pulses on the vein and, thus the greater the increase in venous flow (47). Degani et al. (24) also discovered a linear relationship between umbilical vein flow and UCI ($r=0.59$, $p=0.001$), but no correlation was noted between Doppler characteristics in the umbilical arteries and UCI. However, a three-dimensional computer simulation tool for blood flow in the umbilical artery revealed that increased coiling necessitates a considerable rise in pressure gradient to keep a given blood flow because of the impact of coiling on the streamlining of flow and wall shear stresses (48). Yet another cross-sectional study conducted in Japan showed that umbilical artery and venous blood flow are not affected by UCI at 11-13 weeks of gestation (49). Further standardized studies might answer this disparity and help in reaching firm conclusions.

As mentioned earlier, the cord's resilience to kinking and compression may be increased by the coils, but the reverse was observed under a strong encircling force. Georgiou et al. (50) conducted an experiment with standardized tight encirclement pressure to measure venous perfusion and noted an inverse correlation between UCI and the minimal weight needed to plug venous perfusion. One more interesting characteristic is that the variations in blood flow parameters between the hyper-, hypo-, and normo-coiled umbilical cords were minimal and statistically insignificant (31). However, potential clinical consequences are unclear and a conclusion about Doppler characteristics cannot be reached with these small studies and no subsequent conclusive studies.

Review and discussion

An all-language literature search was conducted on Medline for the period 1970 to 2023. The following search terms were used: umbilical cord; umbilical coiling; coiling index; abnormal coiling; perinatal outcomes, and cross-referencing yielded further information.

Abnormal coiling (under-, over-, and non-coiling) is associated with an increased risk of several unfavourable perinatal events. Set in early gestation, abnormal coiling develops into a chronic state that can have both acute and chronic implications for the fetus. Several studies have been performed showing these associations.

Maternal age and gravida

Although advanced maternal age is known to be associated with adverse pregnancy outcomes (51), studies have shown that abnormal coiling, either hypocoiling or hypercoiling, was not significantly associated with maternal age (52,53). Similarly, the gravida of the mother had no effect on the likelihood of abnormal coiling (36,43). These findings are consistently reported with no contrary findings reported in the literature we explored.

Gestational diabetes mellitus

Most studies conducted in this field showed a significant association between gestational diabetes mellitus (GDM) and abnormal coiling (54-56), with hypocoiling as the most abnormal pattern found (57). However, some studies showed no significant association between GDM and occurrence of abnormal coiling (58). This disagreement between studies could be attributed to subgroup analysis in their evaluations, as well as population selection.

Pre-eclampsia

Research showed a significant association between pre-eclampsia with both hypocoiled (54) and uncoiled (an extreme form of hypocoiled) cords (55,59). Due to the elastic properties of the coiled umbilical cord, it can withstand

outside forces that could disrupt the vascular flow. In addition, a coiled cord is more resistant to compression, snarling torsion, and stretch than the hypocoiled or uncoiled cords (59,60). This could explain the link between hypocoiling and pre-eclampsia.

Pre-eclampsia is linked to adverse fetal outcomes, such as preterm birth, intrauterine growth retardation (IUGR), low birth weight (LBW), and fetal and neonatal death, and later chronic diseases (61), which independently showed associations with umbilical cord coiling. A study showed an association between excessive coiling and fetoplacental vascular resistance and put forward hypercoiling as a risk factor for preeclampsia (62). The disparity between the findings of these two studies show the large amount of missing information regarding this topic and yet to be explained. This will necessitate multiple future studies.

Abruption (abruptio placentae)

Abruption was documented significantly more often in cases with hypocoiled umbilical cords than in normo-coiled and hypercoiled cords (35,54). The close association between abruption and preeclampsia is most probably the reason for this finding (54).

Maternal thyroid disease

Maternal thyroid disease (hypothyroidism and hyperthyroidism) and abnormal umbilical coiling had no significant association, according to a study done in 2018 (57). However, with only one study conducted so far, no robust conclusions can yet be drawn.

Maternal iron status

Following a rise in erythrocyte count in the placental villous circulation, de Laat et al. (63) discovered that increased coiling was connected to prolonged fetal hypoxia/ischemia. Deficient maternal iron status (lower serum ferritin and lower total body iron values) might cause fetal anaemia and, subsequently, hypoxia, which means that hypercoiling may have relevance in mothers with abnormal iron status. Steinl et al. (46) also reported that hypercoiling was associated with lower maternal iron status.

UCI scores and cord blood transferrin saturation were found to be positively correlated by Namli Kalem et al. (64), although there was no connection between UCI and maternal ferritin. However, this difference was due to the use of linear correlation analysis instead of using categories of UCI because the aim was to investigate factors affecting umbilical coiling. The connection between hypercoiling and iron status needs to be explained in more comprehensive investigations with larger sample numbers.

Vascular endothelial growth factor A

Vascular endothelial growth factor A (VEGFA), an angiogenesis regulator, is necessary during the prenatal period for trophoblast proliferation, endothelial cell migration, embryonic vasculature development, and maternal and fetal blood vessel enlargement in the uterus, vasodilation, and angiogenesis. We found only one study investigating the association between VEGFA and abnormal coiling and this concluded that abnormal coiling patterns appear to be related to the down-regulation of VEGFA (65).

Oligohydramnios and polyhydramnios

Oligohydramnios has been significantly associated with hypocoiling (37,54) whereas polyhydramnios was significantly associated with hypercoiling (54). Edmond's hypothesis (1) is the answer to this observation. This hypothesis suggests that the rotating movement provided to the embryo causes the twist of the umbilical cord, and therefore the larger the fluid amnii, the greater the rotary movement of the fetus, and hence the coiling. The opposite is true for oligohydramnios. However, a large number of studies are needed to provide conclusive evidence about this association. Currently there are a limited number of studies with small samples and thus it is not possible to comment on these associations with any certainty.

Fetal heart rate variations

Studies have consistently shown a significant correlation between fetal heart rate abnormalities and both hypercoiled and hypocoiled umbilical cords (37,54,66,67). Abnormal coiling being less flexible and more prone to torsion and kinking, means these are less able to tolerate the stress of labor compared to normocoiled cords (67). As stated in the latter part of this article, this observation might also explain increased interventional deliveries in abnormal coiling, as interventional deliveries are used for fetuses with heart rate abnormalities.

Small for gestational age and intrauterine growth restriction

SGA is defined as a birth weight of less than the 10th percentile for gestational age while IUGR is defined as a rate of fetal growth that is below normal. Abnormal coiling was consistent with both SGA and IUGR babies (52,68,69), with most studies supporting this.

Studies such as Machin et al. (60) and Strong et al. (67) showed that hypocoiling was associated with SGA and IUGR and concluded that hypocoiling eventually reduces fetoplacental circulation, which limits growth. This association was also noted by Chitra et al. (54). However, studies such as that of Ezimokhai et al. (55) and others reported an association between hypercoiling and both SGA and IUGR (43,50,53). This

fact that both under- and over-coiling of the umbilical cord may be associated with both SGA and IUGR is not yet explained. Irrespective of the type of abnormal coiling, it is not wrong to say that abnormal coiling is significantly associated with SGA and IUGR.

Ponderal index

The ponderal score or index (PI) is calculated as weight (kg) divided by cubed height (m^3). As abnormal coiling is linked with fetal growth restriction, the PI is altered in abnormal coiling (43). However, Gupta et al. (59) studied around 100 cords and concluded no association between PI and abnormal coiling. We expect this might be due to the reason that both variables in the calculation of the PI are affected in the same direction by abnormal coiling and PI is a ratio of these two variables.

Intrauterine death and abortion

Only a few studies have been done in this area, but studies consistently showed a notable association between hypercoiling and intrauterine death (IUD) and abortions (70,71). Past research suggested that constriction and torsion occur after fetal death as a result of the maceration process. However, there is a widespread assumption that hypercoiling interrupts fetal-placental circulation and leads to undesirable consequences (71). Furthermore, a similar association is seen between non-coiled umbilical cords and an increased risk for perinatal morbidity and mortality (67). This might be because of the configuration, as coiling is structurally more resistant to external pressures and this advantage is lost in non-coiled cords.

Fetal presentation

There is little data in the literature to review the relationship between the presentation of fetuses and coiling. Ochshorn et al. (72) claimed the first report on this association and reported that fetuses in the breech presentation have noticeably shorter and less coiled cords and lower mean UCI, while no variation was observed in vertex presentation. The precise cause or causes of these differences are as yet unknown.

Mode of delivery

Umbilical cords with UCI values >90th percentile and <10th percentile were significantly associated with lower segment caesarean section than umbilical cords with UCI between 90th and 10th percentiles (37,43,54). Though such an association was discovered in the majority of studies, the underlying cause is not explained in the literature. However, UCI may not be directly related to the mode of delivery but to adverse clinical outcomes, which influence the mode of delivery.

Preterm birth

Preterm birth is a live birth that occurs before 37 completed weeks of pregnancy. Similar to SGA and IUGR, abnormal coiling was significantly associated with preterm birth (36,69,73). The majority of the studies showed that hypocoiling was significantly linked to preterm birth (35,37,54,67), but these studies couldn't provide a convincing reason for this finding. Rana et al. (74) and de Laat et al. (63) revealed a connection between preterm birth and hypercoiling. According to these findings, hypercoiling is an adaptive response to fetal hemodynamic alterations that produce premature labor when a particular threshold is crossed.

In addition, the presence of meconium was found to be more strongly associated with abnormal coiling than with normal coiling of umbilical cords (35,43,55,59,68). However, none of the studies provided a specific explanation for the finding. A meta-analysis and a sequential analysis performed in 2019 supported the findings of these previous studies (69).

Birth weight

Predanic and Perni (42) showed that antenatal UCI is a good predictor of neonatal birth weight. So, changes in coiling patterns are obvious in LBW (birth weight <2.5 kg) cases (54). The literature shows a consistent association between LBW and hypocoiling (35) and hypercoiling (74,75). Mittal et al. (37) suggested that this association could be due to higher preterm deliveries in the hypocoiled group and a higher count of babies born with SGA in the hypercoiled group.

APGAR scores

de Laat et al. (53) and other studies found that low APGAR scores at 1 minute and 5 minutes are significantly associated with UCI <10th percentile compared to normocoiled cords (43,59,68,73). Sharma et al. (35) noted a prominent association between hypercoiling and low APGAR scores at 1 minute and 5 minutes. The association of low APGAR scores with hypocoiling was explained by Georgiou et al. (50) as an inverse relationship was noted between the UCI and the minimum load required to plug venous perfusion, implying that hypocoiling may contribute to compression, as well as kinking, resulting in low APGAR scores. Nevertheless, the authors provided no explanation for the link between low APGAR scores and hypercoiling. Based on these findings, we can conclude that low APGAR scores and abnormal coiling have an association (54,69) and that with larger studies, cause and effect may become clearer.

Neonatal intensive care unit admissions

Babies admitted to the neonatal intensive care unit (NICU) showed a significant association with abnormal coiling, especially with hypocoiling (43,53) and hypercoiling (73) and even with non-coiling (67). However, in one study by Devaru and Thusoo (68) there was no statistical significance in the association between NICU admission and coiling. We believe that the discrepancies between studies are primarily due to different NICU admission criteria, comorbidities, and available local resources.

Conclusion

The umbilical cord has garnered little attention, despite its critical involvement as a connection between placental and fetal circulation. The cord coiling index is preferably determined in the second trimester by observing the middle region of the cord. Studies show that maternal age and gravida were not associated with abnormal coiling. In contrast, a significant association was seen with SGA, IUGR, preterm birth, LBW, low PI, IUD, low APGAR scores, fetal heart rate variations, fetal presentation, and increased instrumental deliveries. There were also significant associations with GDM, preeclampsia, and abruption. Limited research has suggested significant associations with maternal iron status, oligohydramnios and polyhydramnios, and down-regulation of VEGFA, but no association with thyroid disease. Several studies have linked abnormal coiling to abnormal perinatal outcomes, but there are differences in hyper- and hypo-coiling which need to be addressed. The umbilical cord coiling characteristic may not be the only significant factor when considering umbilical cord anatomy in terms of fetal outcome. It is unclear if aberrant coiling is the origin of pathology or one of its consequences (cause and effect) and how much clinical significance it has.

The small sample sizes were a major limitation in most of the studies conducted so far and this limitation can be countered by performing large, multicentric studies. Furthermore, interrelationships between various umbilical cord characteristics require further focus in addition to studies on the association between coiling and clinical outcomes.

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What is your diagnosis?

A 23 year-old female, on post-operative day 9 after an uneventful emergency caesarean section because of non-progress of labour, was referred to our facility with surgical site infection. She gave a history of generalised abdominal pain with excessive pain at the incision site, along with purulent discharge from day 3 after surgery with complete gaping of the wound on day 6 after surgery. She had mild pallor, no icterus and was afebrile. Pulse rate was 116 beats per minute and blood pressure 110/70 mmHg. On examination there was complete dehiscence of the caesarean wound with partially intact rectus sheath. The wound was foul smelling with purulent discharge and sloughing. There was a necrotic base, undermined irregular borders with multiple surrounding erythematous lesions. A similar lesion, 4x5 cm in size was also noted in the mid lower back, corresponding to the site of spinal anaesthesia (Figure 1a, b).

Blood investigations revealed haemoglobin 9 g/dL, white blood cell count $18.7x10^9$/L including 90.8% neutrophils, platelets $8.32x10^6$/dL and serum procalcitonin level of 32.3 ng/mL. Liver and Kidney function tests were normal and viral markers were negative. The patient was empirically started on broad spectrum intravenous antibiotic (piperacillin tazobactam 4.5 gm intravenously 8 hourly) with an-aerobic cover (metronidazole 100 mg 8 hourly). Meanwhile, to rule out any underlying dermatological disease, a dermatology opinion was sought and biopsies from the two wounds were sent for histopathology examination.

Wound swab culture revealed growth of *Escherichia coli* and *Enterococcus faecalis* with sensitivity to colistin. Piperacillin tazobactam was stopped and intravenous colistin was started. Blood and urine cultures were sterile. Wound debridement of the surgical site was done twice, on days two and five after admission, under intravenous sedation and local anaesthesia. With continuation of antibiotics and twice daily saline dressings, the sloughing gradually cleared but there was no sign of wound healing or even shrinkage of the wound (Figure 1c). Histopathological examination of the skin biopsies revealed mild spongiosis in the epidermis, infiltration of neutrophils around hair follicles, together with multiple focal neutrophilic collections in the dermis (Figure 1d, e).

It was planned to start the patient on high dose, systemic corticosteroids once the wound was free of infection. An early start of systemic corticosteroid is known to cause rapid stabilization of the disease process (1), however, since the wound was infected with virulent bacteria, initiating high dose systemic corticosteroids could have risked flare up of sepsis and deterioration of the general condition of the patient. Tab prednisolone at 1 mg/kg was started on post-operative day 28 when three consecutive wound cultures had all been negative, and leukocyte count and serum pro-calcitonin returned to normal limits. Both wounds showed rapid clinical improvement with the appearance of granulation tissues and reduction of size. Patient was discharged on oral steroids and with a plan to taper the steroid dose. She was regularly followed up. Complete wound healing with secondary intention was noted on postpartum day 92 (Figure 1f).

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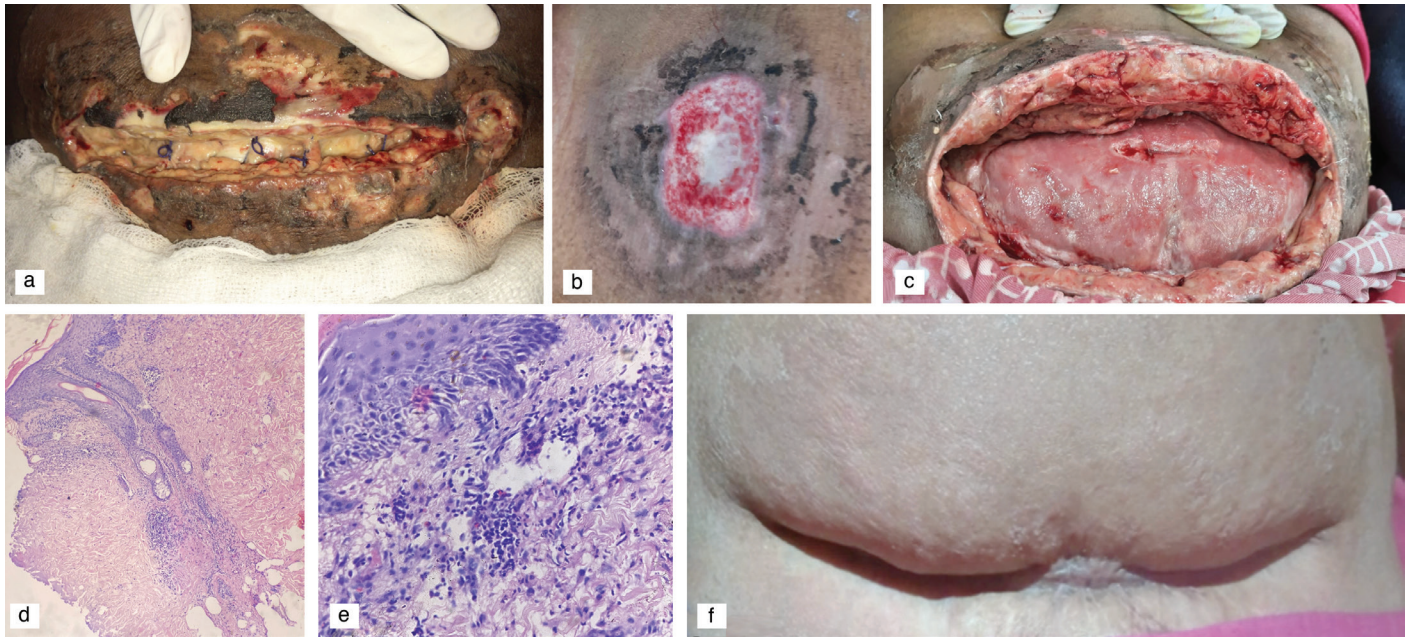

Figure 1. (a). Large gaping wound of the cesarean section; necrotic base, sloughing, purulent discharge, and undermined irregular borders with multiple surrounding erythematous lesions. (b) Wound at the site of spinal anesthesia. (c) Wound after second debridement; significant reduction in sloughing and discharge is evident however there has been an increase in the size of the defect due to pathergy. (d) Section (20x) showing epidermal spongiosis and inflammatory infiltrate around hair follicles with a few focal infiltrates in the dermis. (e) Section (40x) shows focal neutrophilic abscesses in the dermis. (f) Complete wound healing by secondary intention after starting steroids on post-operative day 92

Answer

Histopathological examination was consistent with the diagnosis of pyoderma gangrenosum (PG).

PG is a reactive, non-infectious, inflammatory dermatosis falling under the spectrum of neutrophilic dermatoses. There are several subtypes, with "classical ulcerative PG" as the commonest form, occurring in approximately 85% of cases. This type presents as an extremely painful erythematous lesion which rapidly progresses to a necrotic ulcer with characteristic violaceous undermined edges. Associated symptoms include fever, malaise, myalgia and arthralgia. Healing occurs with an atrophic cribriform scar. Other subtypes include bullous, vegetative, pustular, peristomal and superficial granulomatous variants. Pathergy, the phenomenon whereby skin trauma provokes lesions or the first onset of the disease at the site of injury, is present in 10-40% of PG. The differential diagnosis of PG includes all other causes of cutaneous ulceration and the diagnosis of PG is in reality a diagnosis of exclusion. Underlying systemic conditions are found in up to 50% of cases, with the most common being inflammatory bowel disease and rheumatoid arthritis (1,2).

Post-surgical PG is due to pathergy and the subsequent development of PG lesions at a surgical incision site in the immediate post-operative period. Patients usually present with fever, malaise, and areas of wound dehiscence, that progress to painful ulcers with violaceous, undermined borders, within an average of seven days into the post-operative period. Even though postsurgical PG after breast, chest, cardiothoracic or orthopaedic surgeries are known, reports of the occurrence of PG after caesarean sections are few (3-5) PG should be considered in the differential diagnoses of suspected surgical wound infection (6). In the presented case, the presence of a similar ulcerative lesion at the site of spinal anaesthesia led us to suspect pathergy and consider PG as one of the differentials. The true diagnosis of PG is challenging. Diagnostic criteria for classic ulcerative PG have recently been validated by means of a Delphi consensus of international experts (7). According to this diagnostic model, the one major criterion and 4 of 8 minor criteria are required for the diagnosis of PG.

Major criteria

1. Biopsy with neutrophilic infiltrate.

Minor criteria

1. Exclusion of infection on histology,
2. Pathergy,
3. Personal history of inflammatory bowel disease or inflammatory arthritis,

4. Papule, pustule, or vesicle that ulcerates within four days of appearance,
5. Peripheral erythema, undermining border, tenderness at site of ulceration,
6. Multiple ulcerations (at least one occurring on an anterior lower leg),
7. Cribriform or wrinkled paper scars at healed ulcer sites,
8. Decrease in ulcer size after one month of initiating immunosuppressive treatment.

The Paracelsus score is another novel diagnostic tool for PG (8).

The three major diagnostic criteria include:

1. Progressive disease;
2. Assessment and absence of relevant differential diagnoses;
3. Reddish-violaceous wound border.

Minor criteria include:

1. Amelioration (alleviation) by immunosuppressant drugs;
2. Characteristically irregular shape of ulceration;
3. Extreme pain >4/10 on visual analogue scale;
4. Location of lesion at the site of trauma.

Three additional criteria are:

1. Suppurative inflammation in histopathology;
2. Undermined wound margins;
3. Concomitant systemic disease.

The initial letters of the above-listed criteria form the acronym Paracelsus. Each major criterion is given 3 points, each minor criteria 2 points and each additional criterion 1 point. The sum total score of 10 or more indicates a high likelihood of PG (8).

The treatment of choice for idiopathic PG is systemic corticosteroids. Cyclosporine A, mycophenolate mofetil and tumour necrosis factor-alpha inhibitors are viable second line or adjuvant options (9). In addition, small studies have been published with successful therapeutic intervention using alefacept, visilizumab or anakinra but controlled trials are warranted (10). Although systemic immunosuppressants remain the therapy of choice for most cases of PG, a local approach may also be considered in localized disease. Recently, topical tacrolimus has successfully been used as an off-label drug in localized disease (11).

The role of surgery is controversial because of the risk of pathergy (12). Skin debridement should be avoided in patients with PG, as further surgical insult would only increase the size of the lesion. In the presented case, however, we unknowingly debrided the wound twice due to the presence of the gross infection and sloughing, while awaiting histopathological confirmation. There has been a report of a case of PG after caesarean delivery, which initially mimicked wound infection and was successfully treated with vacuum-assisted closure and split-thickness skin graft. This synergistic approach with vacuum-assisted closure could be an important treatment option for aggressive, wide and slow-healing lesions (13).

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Complete excision of a Skene gland cyst mimicking cystocele

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Abstract

Skene gland abnormalities include skene gland cysts and abscess. These can be differentiated from urethral diverticulum based on clinical findings. The exact incidence of Skene gland abnormalities is unknown as they are relatively rare. They are usually seen in middle-aged female patients but have recently been reported in newborn girls. We present a video case of a large, adult-onset Skene gland cyst, which was evaluated based on clinical findings, radiological aspects and histopathological findings. The differential diagnosis was carried out step-by-step in order to avoid sequelae and complete excision was performed in order to achieve optimal results, both for long-term functional and anatomical outcomes.

Keywords: Cystocele, complete excision, differential diagnosis, Skene gland cyst

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Introduction

Skene glands, also known as the paraurethral glands, are located inferolaterally on either side of the female urethra and are considered the female homolog of the male prostate, originating from the urogenital sinus (1). Skene gland cysts or abscesses have been reported, mostly in prepubertal girls and middle-aged women, but neonatal and congenital manifestations have been reported occasionally (2,3). Skene gland abnormalities are infrequent and the incidence is unknown. Adult-onset Skene gland abscesses/cysts are rare but need to be differentiated from a urethral diverticulum, Mullerian cysts, inclusion cysts, and pelvic organ prolapse (4). A comprehensive urogynecological evaluation is necessary to reach the final diagnosis. Conservative therapy should be the first line treatment but surgical options are available if treatment fails (5-7). Although different surgical interventions have equal success rates, the most effective management is currently unknown. This is a video article (Video 1) of a large, adult-onset Skene gland cyst accompanied by voiding symptoms mimicking cystocele where the differential diagnosis was generated step-by-step and complete excision was performed.

Case study

A 38 years old female, gravida 2 para 2, with no significant past medical history was admitted to our obstetric emergency outpatient clinic with a 30 mm bulge of a submucosal mass originating from the left side of the external urethral meatus, expressing pus and with the appearance of a cystocele (Figure 1). She had a 1-year history of vaginal discomfort accompanied by obstructive voiding symptoms, recurrent urinary tract infections (UTIs) and dyspareunia without resolution after multiple courses of antibiotics and reported feeling a bulge. On physical examination, initial impression was of an approximately 30 mm bulge with the appearance of a grade 2 cystocele. However, closer inspection with speculum examination revealed that the bulge was closely associated with the vicinity of the external urethral meatus in the periurethral area. Pre-operative urogynecological examination of the patient demonstrated that the mass caused the external urethral meatus to deviate to the right side. By manual compression of the cystic mass, pus was seen to discharge from the cyst but not from the external urethral meatus. Perineal ultrasound showed that the mass had no connection with the urethra, despite causing compression of the urethral canal to the right side (Figure 2).

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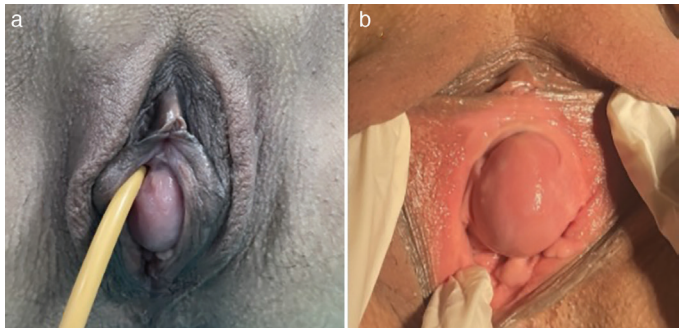

Figure 1. (a) Pre-operative urogynecological examination of the patient illustrating the 30 mm, palpable, round-shaped mass, mimicking a cystocele, which deviates the external urethral meatus to the left side. No pus discharge occurred from the urethral meatus on manual compression of the cystic mass. (b) Physical examination of the patient demonstrating the cystic mass covering the external urethral meatus and causing voiding dysfunction, intermittent urination, dyspareunia, and pain

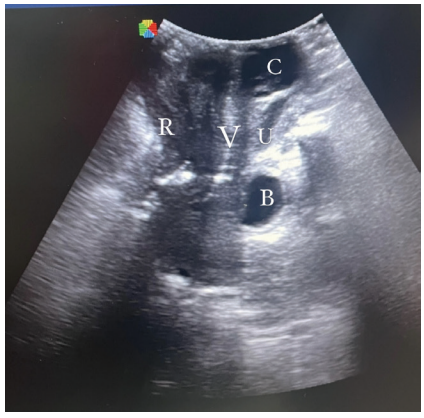

Figure 2. Perineal ultrasonography of the patient illustrating the round-shaped, superficial, cystic structure located inferior to the symphysis pubis. Translabial soft tissue rendered grayscale image demonstrates a mid-sagittal view of the cystic mass, which has no communication with the distal urethra. The mass clearly distorts the position of the urethral meatus
B: Bladder, C: Cyst, R: Rectum, U: Urethra, V: Vagina

Differential diagnoses included urethral diverticulum and occult fistula so contrast magnetic resonance imaging (MRI) and cystogram were performed preoperatively. Intravenous (i.v.) contrast enhanced MRI at the sagittal plane showed that without any diffusion restriction a 3 cm oval periurethral fluid collection was located below the level of the pubic symphysis, consistent with a Skene gland abscess (Figure 3). In addition, the cystogram was performed to eliminate urethral diverticulum and the findings supported the Skene gland diagnosis when no connection of the urethra with cyst wall was found. Skene gland abscess/cyst was considered as

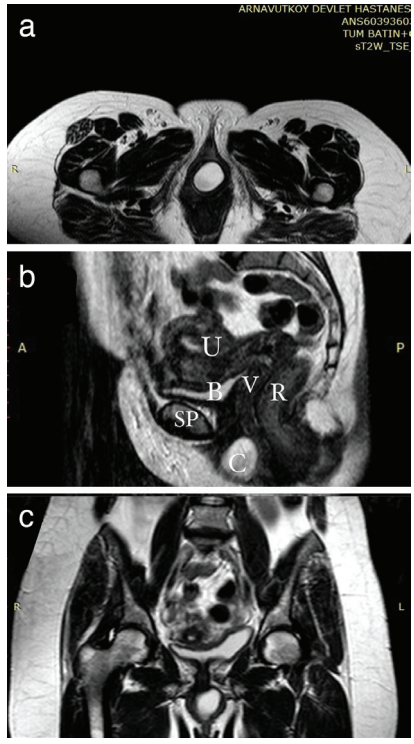

Figure 3. (a) Axial sT2W-Turbo spin echo contrast enhanced magnetic resonance imaging (MRI) showing a 30x27x30 mm cystic mass in the anterior introitus containing T2 hyper-intensity without any connection with the urethra. (b) Sagittal sT2W-Turbo spin echo contrast enhanced MRI showed high-intensity on St2w1 (low-intensity on sT1W1) without any diffusion restriction. A 30 mm oval mass is located inferior to the symphysis pubis and lateral to the external urethral meatus (B: Bladder, C: Cystic mass, R: Rectum, U: Uterus, V: Vagina). (c) Frontal sT2W-Turbo spin echo contrast enhanced MRI demonstrating a well-contoured, cystic mass, located slightly to the left side in the periurethral region

the definitive diagnosis and complete cyst excision planned for the surgical procedure.

The patient underwent cystourethroscopy preoperatively to investigate communication with the urethral lumen. A 19 Fr rigid cystoscope was inserted into the bladder. Upon exiting there was no communication of the abscess with the urethra. Then, a urethral Foley catheter was inserted before the initial surgical incision. An incision was made over the cyst, using traction and countertraction. A fine Medicon scissors was used to mobilize the vaginal epithelium of the underlying cyst. The dissection area was adequately visualized due to intimate involvement between cyst wall and urethra. The abscess was traced on all sides and dissected from the periurethral connective tissue. After complete excision the abscess was drained and the contents sent for culture while the tissue specimen was sent for histopathological assessment. Paraurethral tissues were

approximated with interrupted 4-0 vicryl sutures in order to maintain hemostasis. Extra tissues of the cystic wall were excised and the incision was closed with running-fashion 3-0 vicryl sutures. Histopathological examination of the cystic lesion indicated a benign cyst wall lined with transitional or stratified squamous epithelium.

The patient was admitted to the hospital overnight with a Foley catheter and vaginal packing. i.v. ampicillin treatment continued during hospitalization and one week after surgery. Vaginal packing was removed on postoperative day 1. The patient was discharged on postoperative day 1 with the Foley catheter to a leg bag. Urinary catheterization was left in place for 72 hours after the surgery. The patient was discharged with no complaints, and no complications such as repetition, hematoma, surgical site infection, dyspareunia, or scar formation occurred during the follow-up period. The follow-up period was 24 months including outpatient clinic visits on the first and sixth months and after one and two years. The incisions healed well, the intermittent voiding dysfunction was resolved and no recurrence was reported.

Discussion

Skene gland cystic lesions are typically asymptomatic and are occasionally discovered incidentally during pelvic examinations and in routine urological practice. Clinicians should be suspicious when patients present with recurrent UTIs, chronic urethral pain, and dyspareunia, especially when investigations do not identify any other source (6,8). While some patients may exhibit a visible palpable cyst causing dysuria, pain, and voiding dysfunction, a diagnosis can often be made through physical examination. In contrast to the literature, the presented patient had a 3 cm cystic mass distorting the urethral meatus, resulting in intermittent urination, dysuria, and painful intercourse. Initially, the cystic mass resembled a cystocele upon visual inspection. However, a simple physical examination and speculum examination revealed that this cystic mass originated from the inferolateral aspect of the external urethral meatus. In most cases, a combination of physical examination and history taking is sufficient for diagnosis, although advanced imaging techniques, such as MRI and cystourethroscopy, can be used for differential diagnosis. In contrast to earlier reports, we opted for perineal ultrasonography as a preliminary imaging study. Perineal ultrasonography readily confirmed that the cystic mass had no connection with the distal urethra. Clinicians, particularly gynecologists, may use perineal ultrasonography as a non-invasive screening tool.

During the process of differential diagnosis, clinicians need to rule out malignancy, as there have been a few reported cases of Skene gland adenocarcinoma (9). To distinguish this cystic mass from other periurethral pathologies, the patient's medical history and a thorough physical examination are usually sufficient. One notable characteristic of Skene gland cyst that usually distinguishes it from other pathologies is its potential to displace the position of the external urethral meatus and cause obstructive voiding symptoms (10). Another distinguishing feature during physical examination, which helps differentiate urethral diverticulum or malignancy from Skene gland cyst, is the absence of urinary or purulent drainage through the urethra when pressure is applied to the cystic mass (9,10). Only a direct pus discharge from the cyst will be observed when the Skene gland cyst is squeezed (6).

Several different approaches have been described for Skene gland cyst surgery, such as marsupialization, partial excision or complete excision (5-7). Shah et al. (6) reported 85.3% success rate in resolution of symptoms after complete excision. Foster et al. (7) reported 10 women having periurethral cystic mass with a 3.5 year mean follow-up period with no recurrence and no perioperative complications after complete excision technique. These authors suggested that the marsupialization technique resulted in a high rate of recurrence and re-operations due to remnant cystic tissue. Köse et al. (8) reported 100% success rate after nine partial excisions and one complete excision procedure. Sharifiaghdas et al. (10) conducted a marsupialization procedure in 85 patients and monitored them for an average of 5.5 years. They reported 83 patients (97.6%) cured, while two patients experienced recurrence of cysts after two and four years. The second surgical marsupialization was successful and uneventful.

Due to the large size of a periurethral cystic mass in the presented case, which caused intermittent urination (obstructive symptoms) and painful sexual intercourse, a comprehensive differential diagnosis was undertaken to determine the appropriate treatment for the patient. All available diagnostic methods were used to assess this large cystic lesion. Taking into consideration the patient's sexual activity and the size of the cystic mass, we opted for a total surgical excision as the treatment approach. Furthermore, she presented with a recurring cystic mass and an absence of resolution despite medical intervention. Although we performed complete surgical excision, it is important to acknowledge that this approach is not without potential complications, notably the risk of urethral injury or weakening of urethral muscles.

Conclusion

To the best of our understanding, this report video presents a unique case in which a Skene gland cyst mimicked a cystocele. The purpose of the video was to guide the viewer through the differential diagnosis process. Skene gland cysts are not commonly encountered in daily practice, so it is important to evaluate them carefully to prevent complications and ensure

positive outcomes. Most of these patients are referred to gynecologists and complain of recurrent UTI with or without vaginal mass. If there is an apparent mass, as in this case, the diagnosis can be made clearly. However, most of these cases are misdiagnosed by physicians due to a lack of knowledge or the complexity of the cases. Gynecologists may have limited knowledge about Skene gland abnormalities, so we hope that this video will increase awareness among our colleagues.

Video 1.

https://www.doi.org/10.4274/jtgga.galenos.2023.2023-6-2.video1

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CONGRESS CALENDER

INTERNATIONAL MEETINGS

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

March 07-10, 2024	25th European Congress on Gynaecological Oncology (ESGO), Barcelona, Spain
March 12-16, 2024	Society for Reproductive Investigation (SRI) 71st Annual Scientific Meeting, Vancouver, Canada
April 18-20, 2024	10th Congress of the Society of Endometriosis and Uterine Disorders (SEUD), Geneva, Switzerland
May 02-04, 2024	ASCCP 2024 Scientific Meeting, New Orleans, Lousiana, United States
May 14-16, 2024	14th European Congress on Menopause and Andropause, Florence, Tuscany, Italy
May 15-19, 2024	**21st National Congress of Gynecology and Obstetrics, T.R.N.C.**
May 17-19, 2024	American College of Obstetricians and Gynecologists (ACOG) 2024 Annual Clinical and Scientific Meeting, San Francisco, California, United States
May 18-22, 2024	American Society for Reproductive Immunology (ASRI) Annual Meeting 2024, Houston, Texas, United States
June 10-14, 2024	The Society of Obstetricians and Gynecologists of Canada Annual Clinical Scientific Conference, Edmonton, Canada
June 19-22, 2024	International Urogynecological Association (IUGA) 49th Annual Meeting, Singapore
July 07-10, 2024	European Society of Human Reproduction and Embryology (ESHRE) 40th Annual Meeting, Amsterdam, Netherlands
September 11-13, 2024	XXIX. European Congress of Perinatal Medicine, Vienna, Austria
October 06-09, 2024	34th ISUOG World Congess, Dubai, UAE
October 16-18, 2024	International Gynecologic Cancer Society (IGCS) 2024 Meeting, Dublin, Ireland
October 19-23, 2024	American Society for Reproductive Medicine (ASRM) 80th Annual Meeting, Denver, Colorado, United States
October 19-22, 2024	19th World Congress on Menopause, Melbourne, Australia
October 27-30, 2024	ESGE 33rd Annual Congress, Marseille, France
November 17-20, 2024	The 53rd American Association of Gynecologic Laparoscopists (AAGL) Global Congress on Minimally Invasive Gynecologic Surgery (MIGS), New Orleans, Lousiana, United States
November 21-23, 2024	The 32nd World Congress on Controversies in Obstetrics Gynecology & Infertility (COGI), Lisbon, Portugal
April 23-27, 2025	**XV. Turkish-German Gynecology Congress, Antalya, Turkey**

CONGRESS CALENDER

NATIONAL MEETINGS

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

March 07-10, 2024	Uludağ Jinekolojik Endoskopi Kampı, Bursa, Türkiye
March 08-10, 2024	11. İstanbul Kadın Doğum Günleri, İstanbul, Türkiye
April 17-21, 2024	Kadın Sağlığı Dernekleri Federasyonu (KSDF) Kongresi, Antalya, Türkiye
May 31-June 01, 2024	**TAJEV Obstetrik ve Jinekolojide Güncel Yaklaşımlar Kongresi, İstanbul, Türkiye**
May 31-June 02, 2024	Ulusal Expermed Kongesi, İstanbul, Türkiye
September 06-08, 2024	3. Uluslararası Pelvik Taban ve Kozmetik Jinekoloji Kongresi, İstanbul, Türkiye
September 18-22, 2024	7. Minimal İnvaziv Jinekolojik Cerrahi Kongresi, İstanbul, Türkiye
October 02-06, 2024	6. Jinekoloji ve Obstetrikte Tartışmalı Konular Kongresi, Antalya, Türkiye
November 14-17, 2024	12. Üreme Sağlığı ve İnfertilite Kongresi, Antalya, Türkiye