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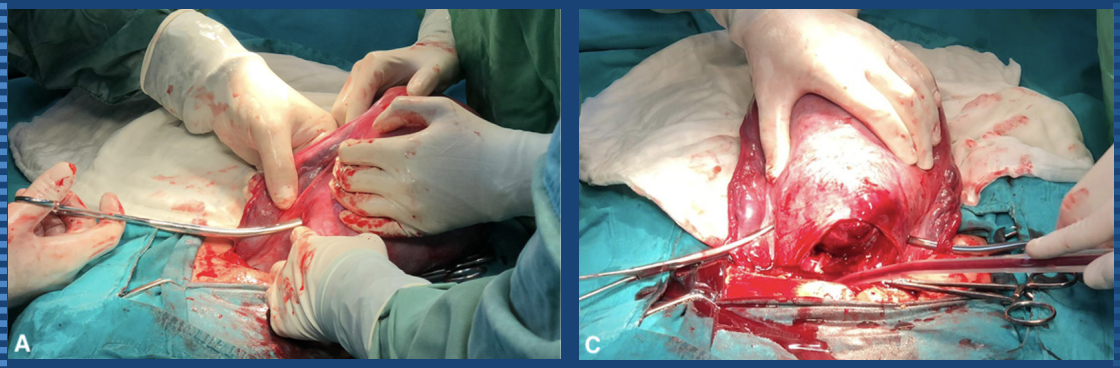

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Cover Picture: Çepni et al. Çepni modification of caesarean section

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Aims and Scope

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

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

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

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The main document and the tables, should be prepared with "Microsoft Office Word software". Times New Roman font (size 12) should be used throughout the main document with 1.5 line spacing. The side margins of the main document should be set at 25 mm from all sides.

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PRISMA for preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/),

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al, for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/),

STROBE statement-checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/),

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A separate title page should be submitted with all submissions and should include the title of the article, name(s), affiliations and major

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

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

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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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Book chapter;

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

Book;

Kohler G; Egelkraut H. In Kohler G and Egelkraut H (edts).Munchener Funktionelle Entwicklungsdiagnostik im zweitem und drittem Lebensjahr. Handanweisung. Munchen: Uni Munchen, Institut fur Soziale Paediatrie und Jugendmedizin; 1984.

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- The Journal name should be abbreviated as "J Turk Ger Gynecol Assoc"

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Contents

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Editorial

Dear Colleagues,

It is my great pleasure to introduce the second issue of the "Journal of the Turkish-German Gynecological Association (J Turk Ger Gynecol Assoc)" in the publishing year of 2025. This issue is consisted of seven articles, and two reviews that we hope you will read with interest. Also you may have the oppurtunity to read the quiz. Here we share some of our favorite articles that were published in this issue of the journal.

Numerous epithelial lesions and malignancies, primarily on cutaneous and mucosal surfaces, are caused by the human papillomavirus (HPV). There is a wealth of evidence connecting HPV to cervical cancer. HPV infection is the cause of almost all cervical cancer cases, with HPV 16 and 18 being responsible for the majority of malignancies. The less common HPV strains linked to cervical cancer also exhibit some regional variation. A study examining the prevalence and significance of multiple strain HPV positivity in patients with cervical preinvasive lesions and cancer will be available for you to read.

Stress urinary incontinence (SUI) in women is a widespread yet undertreated issue worldwide. As recommended, lifestyle changes, pelvic floor muscle exercise and topical vaginal estrogen are usually the first steps in treatment. Those who do not respond well, or who wish to have surgery, can proceed with procedures targeted at the specific mechanism of urinary incontinence. You will also have the opportunity to read an article evaluating the short-term effects of the mini-sling procedure in patients with SUI by performing ultrasonographic examinations and validated questionnaires over a 6-month follow-up period.

Dear Participants,

I am very proud to say that the 15th Turkish-German Gynecology Congress was held in Antalya between April 23-27 of 2025, with a great success with more than 1500 registered participants, 4 precongress courses, 1 live surgery session, 3 keynote lecture, 65 lectures, 6 satellite symposiums, 128 oral presentations, 54 poster presentations and 37 video presentations. It was a tremendous health education event for our community.

We received many positive comments from the congress participants on the quality of the scientific presentations and the organization of the congress. Experts like you who could respond to questions and provide knowledge were crucial to our success. Once again, I would like to express my gratitude to everyone who attended for their time and commitment to this event. Please take note of the dates "**21-25 April 2027**" in your calendars for the 16th Turkish German Gynecology Congress which will be held in Antalya.

Dear Esteemed Readers, Authors and Reviewers,

By choosing to publish in J Turk Ger Gynecol Assoc, you are ensuring that your article can be freely accessed by anyone, immediately on publication. Readers will be able to download and print the article. We encourage all the authors to share their article on social networks, such as Facebook, LinkedIn, and Twitter to disseminate knowledge. Please visit our website at www.jtgga.org, and follow us on Twitter at @JtggaOfficial to stay up to date.

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 Çepni modification: using bilateral vascular clamps during caesarean section for intrapartum hemorrhage, a randomized controlled trial

İsmail Çepni[1], Kübra Hamzaoğlu Canbolat[1], İpek Betül Özçivit Erkan[2], Uğurcan Sayılı[3], Bahar Yüksel Özgör[4], Elifnur Özak[5], Aytaç Mahmudova[6], Rıza Madazlı[1], Kutsiye Pelin Öcal[1]

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Abstract

Objective: Our aim was to reduce blood loss during C-section through the intraoperative temporary occlusion of the bilateral uterine vascular bundles.

Material and Methods: This randomized controlled study included 99 singleton pregnant patients at 37 weeks of gestation or later, with normal fetal development and no obstetric complications, attending a university hospital. In the intervention group (n=45), bilateral occlusion of the uterine vascular bundles at their entry point to the uterus was performed using atraumatic Darmklemmen clamps after the delivery of the baby. In the control group (n=54), routine C-section was performed. Our primary outcome was the amount of blood loss, measured using the suction canister, gauze and abdominal mops and underpads after the operation, along with the comparison of preoperative and postoperative hemoglobin and hematocrit values. Our secondary outcomes were operative time, transfusion rate, maternal outcomes (including postoperative complications during follow-up), and neonatal outcomes.

Results: In the intervention group, blood loss measured in gauze, abdominal compress pads, underpads and total blood loss were significantly lower than in the control group (p=0.031, p=0.001, p=0.003, and p=0.010, respectively). The mean decrease in hematocrit value was 5.3±2.67% in the intervention group and 4.85±2.53% in the control group (p>0.05). Operative time and neonatal outcomes were similar between the two groups. No perioperative or postoperative complications were observed during follow-up.

Conclusion: Bilateral temporary occlusion of the uterine vascular bundles using atraumatic clamps was a feasible and safe technique for reducing blood loss during cesarean section without adverse maternal and neonatal outcomes. Trial registration number and date of registration: NCT05948436- July 10, 2023 [J Turk Ger Gynecol Assoc.2025; 26(2): 73-81]

Keywords: Cesarean section, obstetric hemorrhage, postpartum hemorrhage, surgical clamp, uterine artery

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Introduction

Obstetric hemorrhage, the most common obstetric complication, occurs in 1-3% of births and accounts for 25% of pregnancy-related maternal deaths (1). Although the World Health Organization (WHO) recommends limiting the cesarean section rate to 10-15 per 100 live births, global cesarean section rates continue to rise (2). The classic definition of postpartum hemorrhage is an estimated blood loss (EBL) exceeding 500 mL following vaginal delivery and 1000 mL following cesarean section. Cesarean delivery increases the risk of obstetric hemorrhage compared to vaginal delivery. However, in 2017, the American College of Obstetricians and Gynecologists revised this definition of blood loss to: an EBL of ≥1000 mL, regardless of delivery mode, or blood loss accompanied by symptoms of hypovolemia within 24 hours of delivery (3).

The incidence of severe postpartum hemorrhage has risen due to an increased risk of placenta previa and placenta accreta spectrum, conditions strongly associated with rising cesarean section rates, which currently account for 18.6% of all deliveries (4). To date, no cesarean section technique has been found to be superior in reducing uterine bleeding (5). Pharmacological, mechanical, and surgical methods can be employed to minimize uterine bleeding (6). Surgical approaches, performed after placental delivery, include compression sutures, bilateral uterine artery ligation, hysterectomy, and pelvic tamponade. However, permanent vessel ligation can lead to complications, such as uterine synechiae following uterine artery ligation (7) and ischemic complications, like buttock and bladder necrosis after internal iliac artery occlusion (8). Therefore, new and less invasive methods are necessary to reduce postpartum hemorrhage-related morbidity and mortality during cesarean section.

At term, uterine blood flow reaches to 600-900 mL/minimum (min), accounting for approximately 10% of cardiac output (9). Following delivery through a Munro-Kerr incision during cesarean section, reducing uterine blood flow from the uterine arteries is crucial to prevent intra- and postpartum bleeding. Therefore, the aim of this study was to decrease intraoperative bleeding during classical cesarean section by temporarily occluding the bilateral uterine vascular bundles with atraumatic clamps externally after the baby was delivered.

Material and Methods

This study was designed as a randomized controlled trial following the CONSORT guidelines. It was registered on clinicaltrials.gov.tr with the NCT number of NCT05948436. The full trial protocol can be accessed at https://clinicaltrials.gov/study/NCT05948436.

The study was approved by the Ethics Committee of Cerrahpaşa Faculty of Medicine, İstanbul University-Cerrahpaşa Ethics Committee (approval number: 37612, date: 04/02/2020).

Pregnant patients requiring cesarean section who met the inclusion criteria were enrolled between July 2023 and September 2023. Patients were randomly allocated into two groups (intervention and control) using a 1:1 ratio. Detailed information about the procedure was provided, and informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Demographic characteristics, including age, gestational age, gravidity, parity, mode of previous deliveries, and maternal comorbidities, were recorded. In addition, preoperative, intraoperative and postoperative parameters, including (EBL, mL, gr) were recorded.

The EBL was determined using the gravimetric method. All gauzes, abdominal mops (used from the initial uterine incision until peritoneal cavity closure), and underpads (placed under the patient before surgery and removed at the end of the operation) were weighed and their tare weight was subtracted. The weights were measured in each case after the patient was removed from the operating table and taken to the recovery area. Standardized gauzes and abdominal mops were used, and measurements were taken using a precision balance capable of measuring to two decimal places (10). Blood loss in the suction canister was measured in grams and milliliters. To prevent bias due to amniotic fluid contamination, suctioning was performed before the delivery of the baby, and blood loss measurements were taken afterward. Preoperative (measured the day before surgery) and postoperative (measured the day after surgery) hematocrit and hemoglobin levels, as well as systolic and diastolic blood pressure values, were recorded. Patients were followed until discharge, which occurred on the second postoperative day.

Participants

Nulliparous pregnant patients at 37 weeks of gestation or above, with normal fetal development, no obstetric complications and scheduled for cesarean section were included in the study. The indications for cesarean section included malpresentation, cephalopelvic disproportion and non-reassuring fetal status. Patients with were excluded amniotic fluid volume abnormalities, multiple pregnancy, threatened preterm birth, preeclampsia, placenta previa, placental invasion anomalies and those with comorbidities, such as maternal obesity (body mass index >30 kg/m^2), cardiovascular disease, hypertension, or coagulation defects. Patients using anticoagulants for any indication were also excluded. Moreover, patients who underwent cesarean section during active labor, required general anesthesia, or had a history of previous uterine

surgery were also excluded. Furthermore, any patient in either the control or intervention group who required the use of compression sutures or other preventive measures for uterine atony was excluded.

Interventions

All surgical procedures were performed by the same team. A Pfannenstiel incision was used for the skin and a Munro-Kerr was used for the uterus in all patients. The control group underwent a routine cesarean section technique. In both groups, patients received 15 units of intravenous oxytocin as a uterotonic agent, and compression forceps were applied to the uterine wound margins immediately after placental removal. In the intervention group, bilateral mechanical occlusion of the uterine vascular bundles was performed after the delivery of the baby but before placental extraction. This temporary mechanical occlusion was achieved using atraumatic Darmklemmen clamps, which were placed at the entry level of uterine vessels into the uterus, corresponding to the level of the Munro-Kerr incision. The pulsation of the vascular bundle including both uterine artery and veins, was palpated before clamp placement to ensure accuracy. There was no specified angle for the clamps, but the clinical aim was to occlude all uterine vessels at the level of the Munro-Kerr incision. Once the Darmklemmen clamps were correctly positioned, the placenta was extracted, and the uterine incision was closed using a double-layer, non-locking technique with size 1 absorbable multifilament suture (Polyglactin 910). The duration of occlusion was recorded, and the clamps were subsequently removed. The surgical procedure was completed after hemostasis was achieved. The procedure is outlined in Figure 1.

Outcome measures

The primary outcome was the rate of blood loss measured by the suction canister, gauze and abdominal mops and underpads after the operation, as well as the comparison of preoperative and postoperative hemoglobin and hematocrit values. Our secondary outcomes included operative time, transfusion rate, maternal outcomes, including postoperative complications during follow-up, and neonatal outcomes.

Sample size

The sample size was calculated with G*Power 3.1.9.7. Based on the data of the study conducted by Daggez et al. (11) with an effect size of 0.6, margin of error $\alpha=0.05$, power of the study (1-β) of 0.8 and the sample size was determined as 90, with 45 in each group.

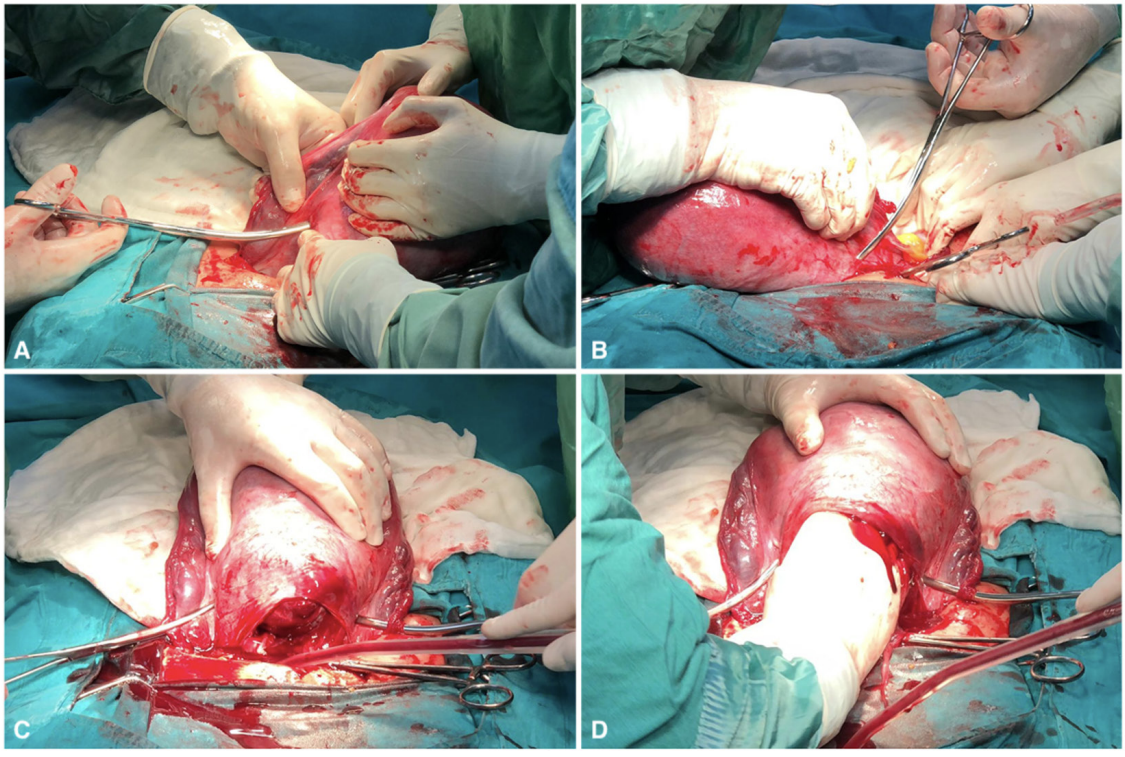

Figure 1. The steps of the Çepni technique during caesarean section: (1) Pfannenstiel incision; (2) Munro-Kerr incision and delivery of the fetus; (3) Temporary exteriorization of the uterus from the abdominal cavity; (4) The bilateral placement of the Darmklemmen clamps to the uterine vascular bundles at the level of Munro-Kerr incision which corresponds to the entrance level of the vessels to the uterus (A, B); (5) The extraction of the placenta (C, D); (6) The double-layer closure of the uterine incision; (7) The removal of the Darmklemmen clamps and control of any injury to the vessels; (8) Bleeding control

Randomization

Patients were randomized in a 1:1 ratio into either the intervention or control group based on their admission order, following a predetermined alternating sequence (first patient to intervention, second to control, third to intervention, and so on). However, to avoid losing participants, patients who declined the intervention were re-assigned to the control group, and recruitment continued until the target sample size for the intervention group (n=45) was reached.

Statistical analysis

Statistical Package for the Social Sciences for Windows, version 21.0 was used for data evaluation and analysis (IBM Corp., Armonk, NY, USA). Categorical variables are presented as frequencies (n) and percentages (%), and numerical variables are presented as the mean ± standard deviation (SD) and median (Q1-Q3). The Shapiro-Wilk test and Kolmogorov-Smirnov test were applied for normality analysis. The chi-square test and Fisher's exact test were used to compare the distribution of the categorical variables between groups. The independent samples-t test and Mann-Whitney U test were used to compare continuous variables between two independent groups. Spearman's correlation was used to assess the relationship between two continuous variables. Finally, a multivariate linear regression analysis was conducted to identify the risk coefficients of the factors for total bleeding. A $p<0.05$ was accepted as statistically significant.

When calculating the EBL, the amount of bleeding measured in mL at the suction canister was multiplied by the density of the blood to standardize the results in terms of units (12).

Results

After 114 patients were assessed for eligibility, 15 patients were excluded because they entered the active phase of labor or required general anesthesia. In total, 99 patients were randomized. Recruitment continued until the required number of patients was achieved in the intervention group, as per the calculated sample size (Figure 2). Of the patients, 54.5% (n=54) were in the control group, and 45.5% (n=45) were in the intervention group (Figure 2). No patients experienced massive

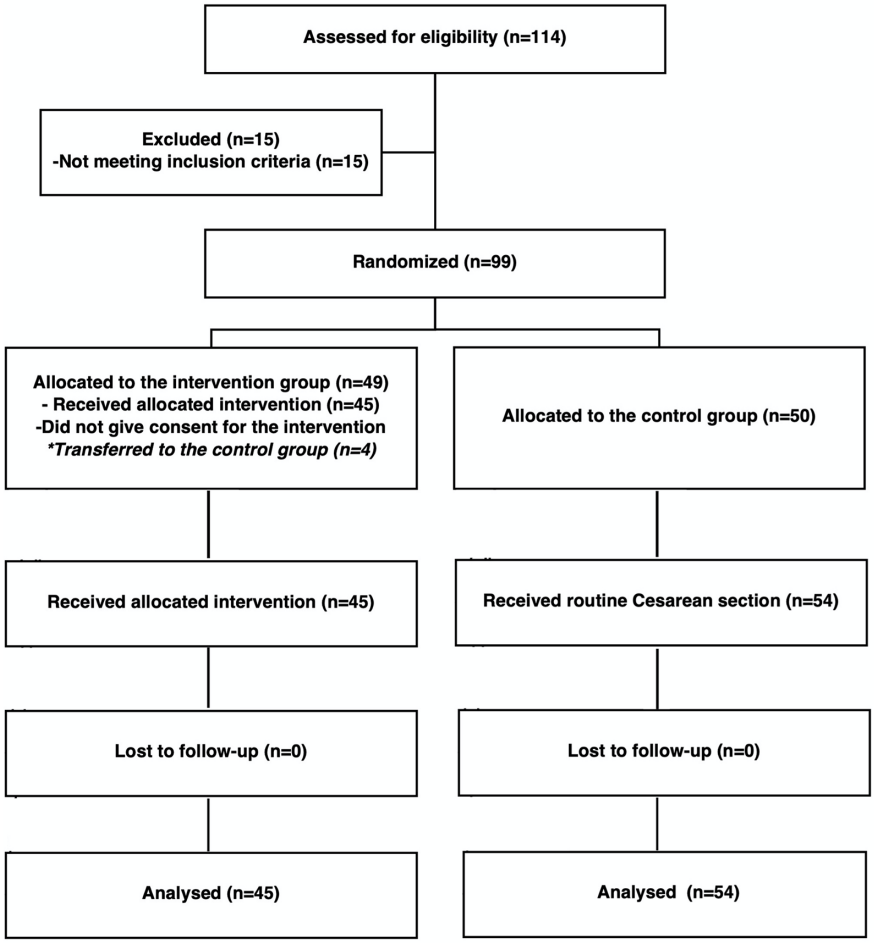

Figure 2. The flow diagram

uterine bleeding that required additional interventions. No patients were lost to follow-up. Recruitment lasted from July 10, 2023 to September 30, 2023. The trial was concluded when the target number of patients was reached.

The demographic and clinical characteristics of both groups are shown in Table 1. Age, gravidity, parity, previous number of deliveries, presence of maternal disease and gestational week were similar between the two groups. The mean age was 30.26±5.67 years in the control group and 29.82±6.35 years in the intervention group.

Pre-, peri- and postoperative parameters are shown in Table 2. All the patients had regional anesthesia. The median dose of intravenous oxytocin was 15 units in both groups (p=0.376). Although not significant, more patients required methylergonovine in the control group (11.1% vs. 8.9%). Not other uterotonic agent, such as carbetosin or misoprostol, were used. The mean drop in hematocrit values was comparable between the two groups, as were the preoperative and postoperative hemoglobin and hematocrit values. While preoperative and postoperative systolic blood pressure and mean arterial pressure values were comparable between the two groups, preoperative and postoperative diastolic blood pressure values were significantly lower in the control group compared to the intervention group (76±10.99 mmHg vs. 81.33±12.11 mmHg, p=0.031 and 70.3±10.3 mmHg vs. 74.72±9.17 mmHg, p=0.048, respectively). No patients in the intervention group required blood transfusion, while two patients (3.7%) in the control group received blood transfusion. The median operative time was 40 (35-45) minutes across the entire cohort and was comparable between the two groups. The median duration of occlusion by the clamp was 11.5 (8-14) min. There was no statistically significant difference between the groups in terms of birth weight or APGAR scores at the 1st and 5th minute. No perioperative or postoperative complications were observed in any patient after the removal of the clamps and during follow-up.

In the intervention group, except for the amount of blood in the suction canister, the amount of bleeding in the gauze, abdominal mops, underpads and total bleeding were significantly lower than in the control group (p=0.031, p=0.001, p=0.003, and p=0.010, respectively) (Table 3). In the intervention group, the median bleeding amounts were 63 g (45-108 g), 99 g (81-135 g), 153 g (126-180 g), 214.65 g (143.1-286.2 g) in the gauze, abdominal mops, underpads and suction canister, respectively. The median total bleeding amount was 535.5 g (437.4-781.2 g) in the intervention group. In the control group, the median bleeding amounts were 99.75 g (63-126 gr), 147 g (105-241.5 gr), 199.5 g (157.5-241.5 gr) and 255.99 g (187.82-389.55 gr) in the gauze, abdominal mops, underpads and suction canister, respectively. The median total bleeding was 728.7 gr (610.05-919.01 gr) in the control group.

There was no statistically significant correlation between total bleeding and preoperative hemoglobin and hematocrit levels. However, a weak negative correlation was observed between total bleeding and postoperative hemoglobin (r=-0.395, p<0.001) and hematocrit (r=-0.386, p<0.001) levels. A weak positive correlation was observed between total bleeding and the magnitude of drop in hemoglobin and hematocrit (r=0.360, p<0.001 and r=0.270, p=0.007). There was no significant correlation between total bleeding and duration of occlusion by the clamp (r=-0.239; p=0.119), whereas a significant correlation was observed between total bleeding time and total operative time (r=0.211; p=0.039).

Table 4 shows the linear regression analysis of the factors that affect total bleeding amount. The intervention and total operative time emerged as independent factors. The

Table 1. The demographic and clinical characteristics of the cohort

		Whole cohort		Control group (n=54; 54.5%)		Intervention group (n=45; 45.5%)		
		Mean ± SD	Median (Q1-Q3)	Mean ± SD	Median (Q1-Q3)	Mean ± SD	Median (Q1-Q3)	p
Age (years)		30.06±5.97	29 (26-34)	30.26±5.67	29 (26-34)	29.82±6.35	30 (25-34)	0.719[a]
Gravidity		2.05±1.37	2 (1-2)	2.13±1.44	2 (1-2)	1.96±1.28	2 (1-2)	0.512[b]
Parity		0.7±0.95	0 (0-1)	0.83±1.06	1 (0-1)	0.53±0.79	0 (0-1)	0.127[b]
Gestational week		38.57±1.21	39 (38-39)	38.56±1.14	39 (38-39)	38.58±1.31	39 (38-39)	0.692[b]
Mode of previous delivery	**ND (n, %)**	11, 29.7 %		5, 22.7%		6, 40.0%		0.295[c]
	CS (n, %)	26, 70.3%		17, 77.3%		9, 60.0%		
Presence of maternal disease	**Absent (n, %)**	50, 50.5%		30, 55.6%		20, 44.4%		0.271[d]
	Present (n, %)	49, 49.5%		24, 44.4%		25, 55.6%		

[a]Independent sample-t test, [b]Mann-Whitney U test, [c]Fisher's exact test, [d]Chi-square test, ND: normal delivery, CS: Cesarean section, SD: Standard deviation

Table 2. Pre-, per- and postoperative parameters of the cohort

		Whole cohort		Control group (n=54; 54.5%)		Intervention group (n=45; 45.5%)		
		Mean ± SD	Median (Q1-Q3)	Mean ± SD	Median (Q1-Q3)	Mean ± SD	Median (Q1-Q3)	p
Intravenous oxytocin (IU/mL)		15.91±2.71	15 (15-15)	15.93±2.19	15 (15-15)	15.89±3.25	15 (15-15)	0.376[a]
Need for methylergonovine	No (n,%)	89 (89.9%)		48 (88.9%)		41 (91.1%)		0.752[b]
	Yes (n,%)	10 (10.1%)		6 (11.1%)		4 (8.9%)		
Preoperative hemoglobin (g/dL)		11.69±1.27	11.8 (10.8-12.7)	11.77±1.26	12 (11.1-12.7)	11.59±1.29	11.7 (10.4-12.6)	0.477[c]
Postoperative hemoglobin (g/dL)		10.13±1.26	10 (9.3-11)	10.04±1.19	10.05 (9.1-10.9)	10.24±1.34	10 (9.5-11.2)	0.418[c]
Drop in hemoglobin (g/dL)		1.62±0.88	1.7 (0.9-2.1)	1.74±0.92	1.75 (1-2.4)	1.46±0.8	1.45 (0.8-2)	0.124[c]
Preoperative hematocrit (%)		35.1±3.34	35.4 (32.7-37.7)	35.16±3.31	35.4 (33.1-37.9)	35.01±3.41	35.2 (32.6-37)	0.824[c]
Postoperative hematocrit (%)		30.12±3.53	29.8 (27.9-32.2)	29.86±3.3	29.6 (27.8-32)	30.42±3.8	29.8 (28-32.7)	0.438[c]
Drop in hematocrit (%)		5.1±2.61	5 (3.3-6.7)	5.3±2.67	5.1 (3.3-7)	4.85±2.53	4.9 (3.1-6.6)	0.397[c]
Preoperative maternal SBP (mmHg)		122.11±13.16	121.5 (111-130)	120.68±14.1	120 (110-130)	123.67±12.02	125 (116-133)	0.284[c]
Postoperative maternal SBP (mmHg)		119.05±10.83	119 (111-126)	118.45±10.03	118.5 (112-124)	119.67±11.69	120 (110-127)	0.621[c]
Preoperative maternal DBP (mmHg)		78.54±11.78	80 (70-86)	76±10.99	77 (68-82)	81.33±12.11	82 (71-90)	0.031[c]
Postoperative maternal DBP (mmHg)		72.48±9.95	71 (66-80)	70.3±10.3	70 (65-75)	74.72±9.17	75 (70-80)	0.048[c]
Preoperative MAP (mmHg)		93.09±11.08	93.33 (84.67-101.33)	90.88±10.79	91.67 (84-96.67)	95.44±11.03	94.67 (87.67-104)	0.052[c]
Postoperative MAP (mmHg)		88.05±9.58	87.17 (82.17-95)	86.47±9.77	86.33 (80.67-91)	89.7±9.21	90.33 (83-97.33)	0.133[c]
Transfusion	No (n, %)	97 (98.0%)		52 (96.3%)		45 (100.0%)		0.499[b]
	Yes (n, %)	2 (2.0%)		2 (3.7%)		0 (0%)		
Operative time (min)		40.6±10.5	40 (35-45)	40.25±9.18	40 (35-45)	41.02±11.96	40 (35-50)	0.766[a]
Duration of occlusion by the clamp (min)		5±5.96	0 (0-10.5)	0±0	0 (0-0)	11.01±3.28	11.5 (8-14)	<0.001[a]
APGAR score (1 min)		7.48±1.31	8 (7-8)	7.5±1.31	8 (7-8)	7.47±1.32	8 (7-9)	0.852[a]
APGAR score (5 min)		8.76±0.92	9 (8-9)	8.78±0.88	9 (9-9)	8.73±0.96	9 (8-9)	0.667[a]
Birth weight (g)		3260.48±490.53	3305 (2955-3560)	3305.42±455.51	3330 (3060-3640)	3207.56±529.1	3265 (2950-3500)	0.328[c]

[a]Mann-Whitney U test; [b]Fisher's exact test; [c]Independent sample t test, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, Min.: Minute, SBP: Systolic blood pressure

intervention decreased total bleeding by 217 units when adjusted for operative time, age, preoperative hematocrit, and systolic blood pressure. When adjusted for group, age, preoperative hematocrit, and systolic blood pressure, each 1-minute increase in operative time increased total bleeding by 7.1 units.

Discussion

In the present study intraoperative bilateral temporary occlusion of the uterine vascular bundle was performed using atraumatic Darmklemmen clamps after fetal delivery. This procedure significantly reduced the amount of intraoperative and early postpartum bleeding during cesarean section.

Table 3. Estimated blood loss for the whole cohort

	All groups		Control group (n=54; 54.5%)		Intervention group (n=45; 45.5%)		
	Mean ± SD	Median (Q1-Q3)	Mean ± SD	Median (Q1-Q3)	Mean ± SD	Median (Q1-Q3)	p[a]
Gauze (g)	93.95±59.28	84 (52.5-117)	105.58±63.56	99.75 (63-126)	80±50.96	63 (45-108)	**0.031**
Abdominal mops (g)	158.05±117.75	115.5 (90-189)	190.26±131.42	147 (105-241.5)	119.4±85.3	99 (81-135)	**0.001**
Underpads (g)	188.45±94.21	171 (126-220.5)	208.83±105.31	199.5 (157.5-241.5)	164±72.73	153 (126-180)	**0.003**
Amount of bleeding in suction canister (mL)	271.52±185.49	225 (135-367.5)	282.04±189.73	241.5 (177.19-367.5)	258.9±181.59	202.5 (135-270)	0.346
Amount of bleeding in suction canister (g)	287.81±196.62	238.5 (143.1-389.55)	298.96±201.12	255.99 (187.82-389.55)	274.43±192.48	214.65 (143.1-286.2)	0.346
Total (g)	728.28±329.85	665.49 (503.1-898.8)	803.64±361.36	728.7 (610.05-919.01)	637.83±264.01	535.5 (437.4-781.2)	**0.010**

[a]Mann-Whitney U test, mL: Milliliter, g: Grams, SD: Standard deviation

Table 4. The linear regression analysis of the factors affecting total bleeding amount

	B	95% CI	p
Group	-217.074	-355.596/-78.553	**0.003**
Operative time	7.094	0.466/13.723	**0.036**
Age	-3.145	-14.755/8.465	0.591
Preoperative hematocrit levels	-17.205	-39.036/4.626	0.121
Preoperative maternal systolic blood pressure	0.537	-4.861/5.935	0.844

CI: Confidence interval

Although the rate of postpartum hemorrhage has recently risen in developed countries, the rate of peripartum hysterectomy has decreased (13,14). This suggests that the prevention of peripartum hysterectomy due to postpartum hemorrhage is possible with improved facilities and surgical techniques. This new technique was developed to reduce the blood supply to the uterus, which is known to increase during the last weeks of pregnancy. Our technique reduced the total amount of bleeding without increasing the operative time, postoperative complications, and worsening maternal and neonatal outcomes. However, the drop in hemoglobin and hematocrit values and transfusion rates were not affected by using our technique. Sudden changes in hemoglobin and hematocrit values may not be evident immediately after a cesarean section due to the hemodynamic changes that occur as pregnancy ends. The resolution of edema, changes in heart rate, stroke volume, and other factors all affect the hemodynamic stability of patients. Therefore, the decrease in intraoperative total bleeding may not be reflected in postoperative hemoglobin and hematocrit values.

This is the first study where the uterine vascular bundles were temporarily clamped during a cesarean section to reduce the amount of bleeding. There are studies describing the clamping of the internal iliac artery in patients diagnosed with abnormal placental invasion (11,15,16). In the study of Yang et al. (15), clamping was performed after fetal delivery. Although it was shown to reduce the amount of bleeding in cases of placenta increata, its benefit was limited for cases of placenta percreta. Like our technique, Daggez et al. (11) temporarily clamped the internal iliac artery after the delivery of the baby but before the extraction of the placenta and found that the amount of bleeding was reduced in cases with abnormal placental invasion. In contrast, our aim was to reduce the amount of bleeding by clamping the uterine vascular bundle in uncomplicated cesarean sections of singleton pregnancies without any severe obstetric complications.

Ligating or occluding the internal iliac artery would diminish the blood supply to the uterine, cervical, and vaginal vessels due to its branching pattern. Since our goal was to reduce the blood supply to the uterus only, occlusion of the uterine artery would serve this purpose. Thus, we confirmed our hypothesis. In addition, dissection and ligation of the internal iliac artery are complicated procedures that require expertise compared to the clamping of the uterine vascular bundle. In their meta-analysis, which included 795 patients with placenta accreta spectrum, Nabhan et al. (17) concluded that uterine artery ligation significantly reduced the amount of bleeding, while internal iliac artery ligation did not have any significant effect. In the present study, the amount of bleeding was significantly reduced by uterine vascular bundle clamping in elective cesarean sections. The advantage of our technique is that the clamping could be performed temporarily without

requiring dissection, thus avoiding the risk of complications, such as vascular injury. No perioperative and postoperative complications were observed. However, since the success of our technique is highly dependent on the experience of the surgeon, a firm conclusion could only be drawn after more data using this technique becomes available when carried out by other surgical teams and in different populations.

Postpartum hemorrhage is associated with high mortality and morbidity. Since the surgical management of postpartum hemorrhage requires expertise, patients at high risk for bleeding, such as those with placenta accreta spectrum, are recommended to be operated on by gynecological oncologists (9). The occurrence of peripartum and postpartum hemorrhage is, however, unpredictable and can occur not only in high-risk pregnant patients, but also in uncomplicated pregnancies. Therefore, our aim was to reduce intraoperative and early postpartum bleeding with a simple technique that may be performed by any obstetrician without the presence of a gynecological oncologist. However, the success of this technique should also be confirmed in cases with placenta previa and placental invasion anomalies. Even though no cases of thromboembolism were observed, to avoid the complications of prolonged clamping, the optimum duration of clamping should be investigated in animal studies by observing the histological effects and inflammatory responses on a molecular level, in the artery and vein.

The method for measuring EBL during cesarean section is controversial. Various quantitative and semi-quantitative methods have been published, including disposable visual estimation, direct measurement, the gravimetric technique, spectrophotometry, dye dilution technique, radioactive tracer injection, shock-index method, red blood cell counts, and hemoglobin levels (18,19). We opted for the gravimetric technique due to the resources available to us. Previous research has validated this method, demonstrating a correlation with actual EBL (10). Towards the end of pregnancy, maternal adaptation leads to increased blood flow in the uterine arteries, reaching rates of 600-900 mL/min. In light of this, uterine vascular bundle clamping was anticipated to reduce blood loss, which our findings support. However, it will be important to confirm the results of our study with other methods to ascertain the accuracy of blood loss determination.

Study limitations

The strengths of our study include the sufficient sample size to power the study, randomized design, and objective methods for measuring total bleeding. Moreover, we made sure to perform the clamping after the fetus was delivered to avoid any fetal complications. To avoid bias, all surgeries in the study were performed by the same team for planned and uncomplicated cesarean sections (20). However, since the success of this technique is highly dependent on the skill of the surgeon, we could have designed this study as a multi-center project and compared the results of different groups to generalize our findings.

Conclusion

We demonstrated that Çepni modification of cesarean section is safe and effective in reducing the amount of intraoperative and early postpartum bleeding during caesarean section without adverse maternal and neonatal outcomes. Bilateral temporary occlusion of uterine vascular bundle by atraumatic Darmklemmen clamps may be routinely performed as a prophylaxis for intra- and early postpartum hemorrhage in uncomplicated cesarean sections. We believe this technique will reduce postpartum bleeding and, consequently, the rate of peripartum hysterectomy, as well as maternal morbidity and mortality.

Ethics

Ethics Committee Approval: *The study was approved by the Ethics Committee of Cerrahpaşa Faculty of Medicine, İstanbul University-Cerrahpaşa ethics committee (approval number: 37612, date: 04/02/2020).*

Informed Consent: *informed consent was obtained from all participants in accordance with the Declaration of Helsinki.*

Footnotes

Author Contributions: *Surgical and Medical Practices: İ.Ç., K.H.C., İ.B.Ö.E., R.M., K.P.Ö., Concept İ.Ç., Design: İ.Ç., Data Collection or Processing: K.H.C., İ.B.Ö.E., B.Y.Ö., E.Ö., A.M., Analysis or Interpretation: U.S., Literature Search: R.M., K.P.Ö., Writing: İ.Ç., K.H.C.*

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

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Determining the optimal follow-up protocol after primary surgery in patients with early-stage endometrial cancer

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Abstract

Objective: The aim of this study was to investigate the timing of recurrence in patients with early-stage endometrial cancer and to determine the optimal postoperative follow-up protocol for the detection of recurrence.

Material and Methods: Patients with stage 1 and 2, grade 1-3 endometrioid type endometrial cancer who underwent follow-up for at least two years were included. The diagnostic method for recurrence was analyzed for each patient. Analysis of risk factors for recurrence were done using SPSS. Sensitivity analyzes were performed comparing the diagnostic methods.

Results: A total of 303 patients were included and recurrence was diagnosed in 17 (5.61%). Cumulative risk of recurrence was 3.06% in the first 23 months, rising to 7.52% in the first 33 months. Sensitivity of physical examination (PE) was 50.00%, specificity 99.52%, positive predictive value 88.89%, negative predictive value 96.30% and accuracy rate 96.00% respectively. It was found that each step increase of grade increased recurrence odds by 2.549 times [95% confidence interval (CI): 1.078-6.027; p=0.033] while each step increase of stage increased recurrence odds by 2.943 times (95% CI: 1.270-6.820; p=0.012).

Conclusion: It is notable that recurrence rate increased after 25 months and the risk of recurrence increased as the tumor stage and grade worsened. Symptoms in patients with high-grade and deep myometrial invasion, especially after the first two years, should be considered risky and patients should be informed about seeking medical care when symptoms occur. PE and symptoms of patients are key factors in detecting reccurence while other diagnostic methods can be used according to clinical findings. [J Turk Ger Gynecol Assoc. 2025; 26(2): 82-9]

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Introduction

Endometrial cancer is the second most common gynecologic malignancy (1). Endometrial cancer develops in approximately 3% of females in the United States of America (USA) (2). In Türkiye, its incidence was found to be 9.3 in 2009. Since the cancer typically presents with abnormal uterine bleeding, 70% of patients are diagnosed at an early stage (3). Data from the SEER database shows the 5-year survival rate for patients with endometrial cancer to be approximately 95%, but with a significant decrease to 18.9% in cases of metastatic disease (2). Endometrial cancer staging is performed according to the FIGO system, which was revised in 2023 (4,5). The standard surgical treatment involves at least an extrafascial hysterectomy, bilateral salpingo-oophorectomy, peritoneal washing, exploration of the pelvis and abdomen, and biopsy of suspicious lesions. Omentectomy is recommended in high-risk patients. Prognostic factors include age, ethnicity, histological type, tumor grade, myometrial invasion, lymphovascular invasion, cervical involvement, lymph node metastasis, molecular factors (such as POLEmut and p53abn), and positive peritoneal cytology (6).

Most recurrences occur within the first three years, with the vaginal cuff, pelvis, abdomen, and lungs being the most common metastatic sites (7). Local and distant metastases are observed at similar rates. The survival rate in patients with recurrence ranges from 10% to 38% (8). The prior radiotherapy status of the patient is associated with the recurrence rate and survival after recurrence. It has been reported that survival is higher for recurrences that occurred in patients who did not have radiotherapy (6).

Follow-up is recommended in the guidelines at 3-6 month intervals for the first two years, 6-12 month intervals up to five years, and then annually (9,10). The detection of relapses after two years may be delayed by extended intervals. It is improbable that frequent follow-up of asymptomatic patients during the follow-up period will result in the detection of recurrence. There is an absence of evidence that a specific examination method can detect recurrence in asymptomatic patients. Moreover, intensive follow-up has been demonstrated to have no effect on OS, even in high-risk patients. The British Gynaecological Cancer Society advocates a dual approach, integrating symptom-based and patient-based follow-up methodologies (6,9,11,12). Seventy-five to eighty percent of recurrences are detected during physical examination (PE), and half of the patients are symptomatic.

Reducing follow-up intervals increases costs and complicates patient compliance, while longer intervals may lead to late diagnosis of recurrence. The goal of follow-up is to detect recurrences early and prolong survival. However, there is no proven optimal follow-up protocol. Seventy percent of patients with recurrence are symptomatic, and most recurrences are detected by PE. CA-125 levels, smear, and imaging methods used in follow-up have limited success in detecting recurrence. Therefore, a balanced and effective follow-up protocol is also essential.

The aim of this study was to analyze the recurrence patterns and follow-up methods in patients treated for early stage endometrial cancer in a single center, with the goal of developing a more effective follow-up protocol, including optimal follow-up intervals and diagnostic methods.

Material and Methods

The study included patients with stage 1 and 2, grade 1-3 endometrioid-type endometrial cancer who underwent primary surgical treatment at the Department of Obstetrics and Gynecology at a tertiary referral hospital, between February 2006 and July 2016, and were followed for at least two years. Patients with extrauterine disease confirmed by clinical, imaging, and/or pathological evaluation, those with non-endometrioid histology, and those who could not undergo primary surgery due to comorbidities or received fertility-sparing treatment were excluded. Ethical approval for the study was obtained from the Clinical Research Ethics Committee of Ankara University Faculty of Medicine (approval number: 07-441-18, date: 16.04.2018). After diagnosis was confirmed by endometrial biopsy, patients underwent preoperative evaluation through clinical examination and at least transvaginal ultrasonography as an imaging method. Other imaging modalities including magnetic resonance imaging, positron emission tomography/computed tomography (PET/CT), or CT were also used in the preoperative period, but not routinely.

As data in the new staging system, such as molecular classification and lymphovascular space invasion (LVSI), were not available at the time of the study (2006-2016), the study methodology followed the 2009 staging system (13). Patients included in the study were staged according to the FIGO staging system, and those with stage 1A, 1B, and 2 were enrolled. Patients with pathology reports of endometrioid type, endometrioid type with squamous differentiation, and villoglandular endometrioid type endometrial cancer were included. Tumor histologic typing was performed according to the World Health Organization classification system. Grade 1 tumors were defined as having less than 5% non-squamous or non-morular components, whereas grade 3 tumors were defined as having more than 50% non-squamous or non-morular components. Higher grades were associated with increased nuclear atypia and architectural disorganization of cancer cells. Myometrial invasion was determined based on the distance from the endomyometrial junction to the

deepest point of tumor invasion. Myometrial invasion was considered present when the tumor invaded more than 50% of the myometrium. Tumor grade, presence of myometrial invasion, and lymphovascular invasion were documented by the histopathologist.

Patients were followed up every 3-4 months for the first two years, every 6 months for the next three years, and annually after five years. During follow-up visits, symptom inquiry, pelvic examination, and transvaginal ultrasonography were performed. In addition, vaginal cytology, CA-125 levels, posteroanterior chest X-ray, and other imaging methods were used. Imaging techniques such as CT and PET-CT were typically used when symptoms were present or when suspicious findings were detected during PE. Adjuvant treatments, including external radiotherapy, brachytherapy, and chemotherapy, were planned, based on risk factors, in collaboration with the radiation oncology and medical oncology departments.

Patient follow-up data were collected from medical records and the Case Tracking System of Ankara University Faculty of Medicine. Surgical reports, laboratory results, and imaging findings were reviewed to document follow-up assessments, including CA-125 levels, findings from chest X-ray, PET-CT, CT, and PE, and symptom status. Each recurrence was examined individually, and sensitivity and specificity analyses were performed based on the diagnostic methods used to detect recurrence. For patients with recurrence, sensitivity and specificity analyses were performed for combinations of all diagnostic methods used for the same patient. Disease-free intervals and the timing of recurrences were evaluated in light of the available data.

Statistical analysis

Data analysis was performed using SPSS for Windows, version 11.5 (IBM Inc., Armonk, NY, USA). Descriptive statistics are presented as mean ± standard deviation for normally distributed variables, median (minimum-maximum) for non-normally distributed variables, and number of cases and percentages for nominal variables. For comparisons between two groups, the t-test was used for mean values and the Mann-Whitney U test for median values. When the number of groups exceeded two, analysis of variance was used for comparing mean values, and the Kruskal-Wallis test for comparing median values. Nominal variables were analyzed using Pearson's chi-square test or Fisher's exact test. Correlations between continuous variables were evaluated using the Spearman correlation test for non-normally distributed variables and the Pearson correlation test for normally distributed variables.

Recurrence probabilities were calculated using the Kaplan-Meier method. Factors affecting recurrence time were analyzed with the Log-rank test. Multivariate analysis to identify independent factors influencing recurrence time was performed using Cox regression. A p-value <0.05 was considered statistically significant.

Results

A total of 303 patients with early-stage endometrial cancer were included in the study. Among them, 17 patients (5.6%) experienced recurrence. Table 1 shows the demographic, preoperative pathological and postoperative pathological findings of the groups with and without recurrence in patients with early stage endometrial cancer. The demographic, preoperative, and postoperative pathological findings were compared between the non-recurrence group (n=286) and the recurrence group (n=17). The mean age at diagnosis was 59.3±11.1 years in the non-recurrence group and 63.7±10.4 years in the recurrence group (p=0.114). Parity and preoperative CA-125 levels were also comparable between the two groups (p=0.908 and p=0.977, respectively). Menopausal status did not differ significantly between groups (p=0.242), with 88.2% of patients in the recurrence group being postmenopausal compared to 75.9% in the non-recurrence group. Pathological type compared between the recurrence and non-recurrence groups did not reach statistical significance (p=0.057). However, all patients in the recurrence group had endometrioid-type tumors. Grade distribution was significantly associated with recurrence (p=0.023), with higher recurrence rates observed in patients with grade 2 and grade 3 tumors (58.8% and 29.4%, respectively). The stage of the disease was significantly associated with recurrence (p=0.005). Most patients with recurrence were classified as stage 1B (70.6%), while only 17.6% were stage 1A. Myometrial invasion was significantly more common in the recurrence group (76.5% vs. 39.5%, p=0.003). In addition, LVSI was observed in 60.0% of patients in the recurrence group compared to 25.5% in the non-recurrence group (p=0.004).

Recurrence characteristics, diagnostic approaches and timing of recurrence in patients with early stage endometrial cancer are shown in Table 2. Among the 17 patients with recurrence, the most common location of recurrence was the vaginal cuff (41.1%), followed by the abdomen (35.2%). Bone and inguinal lymph nodes were each affected in 11.7% of cases. The primary diagnostic approach for detecting recurrence PE (47.0%), followed by computed tomography (35.2%). PET scan and pap smear less frequently identified recurrence, with detection rates of 5.8% and 11.7%, respectively. Regarding the timing of recurrence, 23.5% of recurrences occurred in the first year after surgery, while 11.7% were observed in the second and fourth years. The third year had the highest incidence, with 35.2% of recurrences. Late recurrences were detected in 17.6% of patients in the seventh year of follow-up.

Table 1. Comparison of demographic, preoperative pathological and postoperative pathological findings in early stage endometrial cancer patients with and without recurrence

	Non-recurrence group n=286	Recurrence group n=17	p value
Age in years, mean ± SD	59.3 ± 11.1	63.7 ± 10.4	0.114
Parity, n (%)	2.6 ± 2.1	2.6 ± 1.7	0.908
CA 125, IU/mL	20.7 ± 21.3	20.9 ± 16.5	0.977
Menopausal status, n (%)			0.242
Premenopause	69/286 (24.1)	2/17 (11.8)	
Postmenopause	217/286 (75.9)	15/17 (88.2)	
Postoperative pathological findings			
Pathological type, n (%)			0.057
Endometrioid	213/286 (74.5)	17/17 (100)	
Squamous Diffuse	61/286 (21.3)	0/17 (0)	
Villoglandular	12/286 (4.2)	0/17 (0)	
Postoperative pathological findings			
Grade, n (%)			0.023
Grade 1	111/286 (38.9)	2/17 (11.8)	
Grade 2	141/286 (49.5)	10/17 (58.8)	
Grade 3	33/286 (11.6)	5/17 (29.4)	
Stage, n (%)			0.005
Stage 1A	166 /286 (58.0)	3/17 (17.6)	
Stage 1B	106/286 (37.1)	12/17 (70.6)	
Stage 2	14/286 (4.9)	5/17 (29.4)	
Myometrial invasion, n (%)			0.003
No	173/286 (60.5)	4/17 (23.5)	
Yes	113/286 (39.5)	13/17 (76.5)	
LVSI, n (%)			0.004
No	190/286 (74.5)	6/17 (40.0)	
Yes	65 /286 (25.5)	9/17 (60.0)	
LVSI: Lymphovascular space invasion, SD: Standard Deviation			

In the evaluation of factors affecting recurrence, a backward stepwise logistic regression analysis was performed, and the most significant factors were included in the final model. These factors were tumor grade, stage, myometrial invasion, and LVSI. After the final step of the analysis, tumor grade and stage remained as independent predictors of recurrence. The analysis revealed that each increase in tumor grade was associated with a 2.549-fold high-risk of recurrence (95% confidence interval (CI): 1.078-6.027; p=0.033). Similarly, each increase in stage was associated with a 2.943-fold high-risk of recurrence (95% CI: 1.270-6.820; p=0.012) (Table 3).

The sensitivity and specificity of individual and combined diagnostic methods for detecting recurrence were evaluated (Table 4). Among isolated methods, PET had the highest sensitivity (91.67%), followed by CT with 88.89%. PE and CA-125 levels demonstrated relatively lower sensitivity at 50% and 41.67%, respectively, while PAP smear showed the lowest sensitivity (20%). Regarding specificity, PE and pap smear had the highest specificity at 99.52% and 99.37%, respectively, indicating a strong ability to rule out recurrence when the test result is negative. CA-125 levels and CT also showed high specificity at 94.01% and 94.00%. PET scan had a specificity of

Table 2. Recurrence characteristics, diagnostic approaches, and timing of recurrence in patients with early-stage endometrial cancer

Variables	Recurrence group n=17
Location of recurrence, n (%)	
Vaginal cuff	7/17 (41.1)
Abdomen	6/17 (35.2)
Bone	2/17 (11.7)
Inguinal LN	2/17 (11.7)
Diagnostic approach for recurrence, n (%)	
PE	8/17 (47.0)
CT	6/17 (35.2)
PET scan	1/17 (5.8)
Pap smear	2/17 (11.7)
The year the recurrence developed, n (%)	
1st year	4/17 (23.5)
2nd year	2/17 (11.7)
3rd year	6/17 (35.2)
4th year	2/17 (11.7)
7th year	3/17 (17.6)
LN: Lymph node, PE: Physical examination, CT: Computed tomography, PET: Positron emission tomography	

Table 3. Evaluation of factors affecting recurrence by multivariate logistic regression analysis

	aOR	95% CI	p value
Grade	2,549	1,078-6,027	0.033
Stage	2,943	1,270-6,820	0.012
The model was established by backward stepwise logistic regression. Tumour grade, stage, myometrial invasion, and lymphovascular space invasion were included in the model. Factors that remained statistically significant are shown in the table. CI: Confidence interval, aOR: Adjusted odds ratio			

87.50%. When diagnostic methods were combined, the highest accuracy (100%) was achieved using either the combination of PE, CT, and CA-125 or the combination of PE, PAP smear, CT, and CA-125, though the positive predictive value (PPV) was relatively lower in the latter combination (53.33%). The combination of PE and CT offered a balance of high sensitivity (93.33%) and specificity (91.49%), resulting in an accuracy of 91.94%.

The estimated mean time to recurrence was 115.1 months, with a standard error of 3.064. The 95% CI for the mean time to recurrence ranged from 108.10 to 122.22 months. The cumulative hazard rates for recurrence over time are illustrated in Figure 1. When evaluating the cumulative hazard rates for recurrence over time, the risk of recurrence was 0.45% at 5 months, 0.91% at 8 months, 1.86% at 10 months, 3.06% at 23 months, 3.70% at 25 months, 4.41% at 28 months, 5.91% at 30 months, 6.70% at 31 months, 7.52% at 33 months, 8.74% at 46 months, 10.06% at 48 months, 12.87% at 73 months, 15.78% at 76 months, and 18.68% at 77 months. These values represent cumulative risk percentages, meaning that by the end of the 77th month, the expected cumulative risk of recurrence for a patient is 18.68%.

Discussion

There is still no universal follow-up protocol after treatment for endometrial cancer. Follow-up frequency and the use of laboratory and radiological monitoring tests vary between countries. Although patients regularly attend follow-up due to fear of recurrence (14), it has been shown that close monitoring does not improve survival in endometrial cancer (9). While the aim of follow-up is to detect recurrences early and improve quality of life, it may have negative effects. Rustin et al. (15) demonstrated that early detection of recurrence in ovarian cancer did not improve survival, and patients' quality of life was adversely affected by earlier chemotherapy initiation. Moreover, many recurrences give symptoms between follow-up visits, but closely monitored patients tend to wait for their next scheduled visit rather than seek immediate evaluation (16). In the systematic review by Leitch et al. (11), the effectiveness of the patient-initiated follow-up model (PIFU) in low-risk endometrial cancer patients after surgery was investigated. The study reported that PFU provided significant positive effects on patient satisfaction, quality of life and psychological well-being when compared with traditional physician-centered follow-up methods. The study further stated that this model enhances patient autonomy, provides flexibility in accessing healthcare services, and reduces the utilization of costly resources. The findings suggest that a patient-oriented and cost-effective approach to follow-up for low-risk endometrial cancer patients is feasible and offers a valuable alternative to current clinical practices (11). Similarly, The British Gynaecological Cancer Society's publication offers a comprehensive overview of the viability and benefits of the PIFU model in the context of gynecological cancer patient follow-up. The PIFU model empowers patients to self-monitor their symptoms and access healthcare services as required, thereby minimizing routine check-ups and enhancing patient satisfaction. The study's findings offer significant insights that can inform the development of more personalized follow-up protocols and enhance the efficient use of resources in the field of gynecological oncology. In the cohort of endometrial cancer patients, it was suggested that patients in the low-risk

Table 4. Sensitivity and specificity analyses of examination, CT, CA 125, pap smear, PET tomography examinations individually and in combination for the detection of recurrence

	Sensitivity (%)	Specifity (%)	PPV (%)	NPV (%)	Accuracy (%)
Physical examination (PE)	50.00	99.52	88.89	96.30	96.00
Computed tomography (CT)	88.89	94.00	72.73	97.92	93.22
CA 125	41.67	94.01	33.33	95.73	90.50
PAP smear	20.00	99.37	66.67	95.15	94.64
Positron emission tomography (PET scan)	91.67	87.50	84.62	93.33	89.29
PE and CA 125	71.43	93.83	50.00	97.44	92.05
PE and pap smear	66.67	98.72	83.33	96.86	95.91
PE and CT	93.33	91.49	77.78	97.73	91.94
PE, pap smear, CA 125	75.00	91.47	52.17	96.72	89.66
PE, pap smear, CT	93.75	86.49	75.00	96.97	88.68
PE, CT, CA 125	100	92.45	77.78	100	94.03
PE, pap smear, CT, CA 125	100	68.89	53.33	100	77.05
PPV: Positive predictive value, NPV: Negative predictive value					

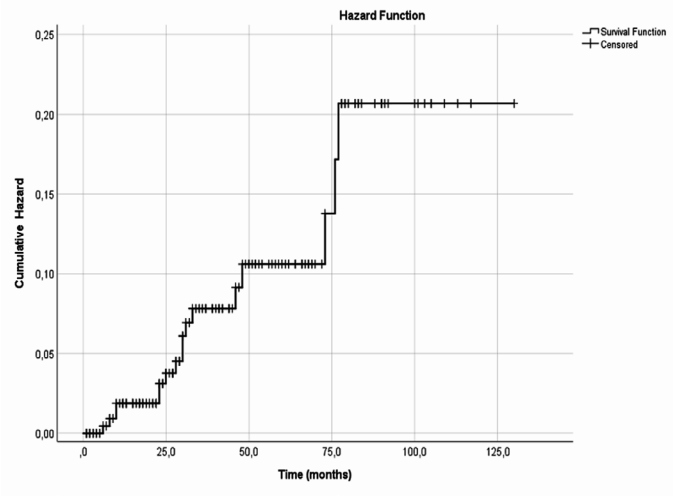

Figure 1. Cumulative assessment of risk ratios of developing recurrence against time

group may be suitable for PIFU shortly after completion of treatment (following a holistic needs assessment), while in the intermediate and high-risk groups, it is safe to switch patients to the PIFU model after the first two years of regular clinical follow-up (12). In another study, Zola et al. (9) compared the effects of intensive and minimalist follow-up regimens on overall survival (OS) after endometrial cancer treatment in the TOTEM trial (9). The study included 1,847 patients, of whom 60% were classified as low-risk. Following a mean follow-up period of 69 months, the 5-year OS rates were 90.6% and 91.9% in the intensive and minimalist groups, respectively, with no significant difference between the two groups. This finding supports the efficacy of minimalist follow-up regimens and suggests the feasibility of less intensive follow-up strategies in the management of endometrial cancer patients (9).

In the present study, which included 303 early-stage endometrial cancer patients, recurrence was detected in 17 patients (5.6%). A recent population-based cohort study in Denmark reported a 7% recurrence rate in stage I-II patients (17), while a 2006 database review, which included all stages, found a recurrence rate of approximately 13% (8).

Several risk factors are associated with a high-risk of recurrence in endometrial cancer. Grade 3 tumors are universally recognized as high-risk, and in our study, both univariate and multivariate analyses demonstrated a significant association with recurrence. Although deep myometrial invasion and LVSI are not universally defined as high-risk, many experts agree that these factors increase recurrence risk. In the present study, both LVSI and deep myometrial invasion were significantly more frequent in the recurrence group.

PE remains essential for detecting recurrences. In the present study, 47% of recurrences were initially suspected based on findings of PE. A review published in 2015 reported that PE had the highest rate of recurrence detection (18%), while vaginal cytology detected recurrence in 1% of cases. Furthermore, 56% of patients with recurrence were symptomatic in the follow-up of 254 patients with high-grade disease. Moreover, elevated levels of the cancer antigen tumor marker CA-125 were detected in 10% of patients (18). Vaginal cytology is widely used in post-treatment follow-up, although its effectiveness is debated. The use of vaginal cytology is no longer recommended for asymptomatic patients in National Comprehensive Cancer Network (NCCN) guidelines. Nevertheless, cytological analysis was historically employed as a means of detecting vaginal recurrences in numerous medical centers. In our protocol, annual vaginal cytology was performed, and two patients (11.1%) with recurrences were diagnosed by cytology. CA-125 measurement has become increasingly popular, although its effectiveness in endometrial cancer follow-up is limited. In our series, preoperative CA-125 levels were within the normal range in two patients with recurrence. Despite this, CA-125 was routinely measured at each visit, but no recurrence was detected based solely on isolated CA-125 elevation. In addition, CA-125 levels can be elevated in many benign conditions, reducing its PPV, which was approximately 33.3% in our series. The NCCN guideline recommends that in patients with initially detected elevated CA-125 levels, the marker should be measured again later (10).

CT is not routinely used in follow-up but was performed when patients were symptomatic or suspicious findings were detected during clinical evaluation. Among patients with recurrence, CT detected recurrence in six (35.2%). Five of these had distant metastases, while one had a local recurrence. A systematic review previously reported that only 5% to 21% of asymptomatic recurrences were detected via CT (8). However, in a study conducted by Jung-Yun Lee et al., it was found that 60% of asymptomatic recurrences were identified via CT scans; four (66.7%) of these patients had localized recurrences and underwent curative-intent surgery, and all of them survived (19). Advances in chemotherapy regimens and surgical techniques may contribute to improved survival outcomes in patients with asymptomatic recurrences detected by CT.

PET/CT is not recommended as a routine follow-up tool due to its high cost. In our center, PET/CT is used for systematic evaluation when suspicious distant or local lesions are detected. Since the installation of PET/CT at our hospital, 12 patients have undergone evaluation for suspected recurrence, with one vaginal cuff recurrence missed by PET/CT. It was found that PET/CT had a sensitivity 95.8% (92.2-98.1) and a specificity of 92.5% (89.3-94.9) for confirming recurrence (20).

Based on our findings, the highest recurrence risk in early-stage endometrioid adenocarcinoma occurs in the first

three years. The recurrence rate increased from 1.86% at 10 months to 3.06% at 25 months, reaching 10.06% at 48 months. Although the risk in the first year is low, follow-up frequency in the second to fourth years should be more intense. Detailed patient education about symptoms requiring immediate medical attention is crucial, especially if considering the PIFU model. PE remains an essential follow-up tool, with a sensitivity of 93.33% and specificity of 91.49% when combined with CT. Larger, randomized studies comparing follow-up intervals and diagnostic tools are still needed to establish an optimal protocol.

Study limitations

The main limitation of the study is that it was conducted using the old staging system. However, as the pathology reports of the patients in the study were recorded using the 2009 staging system, it would not have been appropriate to adjust for the new staging system due to the lack of data, such as molecular classification. Our study has other limitations, including its retrospective design, changes in treatment protocols over the years, and advances in imaging technology that complicate data interpretation. However, the number of patients in our study is comparable to other reports.

Conclusion

The optimal follow-up protocol for early-stage endometrial cancer remains uncertain. Our findings emphasize the importance of risk stratification and individualized follow-up strategies, particularly in the second to fourth years when the recurrence risk is highest. PE should remain a cornerstone of follow-up, supported by targeted imaging when clinically indicated. Future prospective studies with larger patient cohorts are necessary to establish evidence-based follow-up protocols that balance early detection, patient quality of life, and healthcare costs.

Ethic

Ethics Committee Approval: *Ethical approval for the study was obtained from the Clinical Research Ethics Committee of Ankara University Faculty of Medicine (approval number: 07-441-18, date: 16.04.2018).*

Informed Consent: *All patients were informed about colposcopy and follow-up procedures and informed consents were obtained.*

Footnotes

Author Contributions: *Concept: S.T., Design: D.A., Data Collection or Processing: A.G., Analysis or Interpretation: Ş.K.B., Literature Search: B.V., Writing: C.O.U.*

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The histologic results in multiple-type HPV infections

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Abstract

Objective: To evaluate the rate, cytology and histopathological findings of multiple-type human papillomavirus (HPV) positive women referred to a tertiary colposcopy center. To compare the role of multiple- and single-type HPV infections in women with high-grade squamous intra epithelial lesion and cervical cancer (HSIL+).

Material and Methods: The cytological and histopathological results of 2070 HPV positive women were evaluated. Infection with more than one type was defined as multiple-type HPV infection. Patients were divided into single or multiple HPV groups and subgroups in terms of HPV types; and also examined in three age groups. Age-stratified HSIL and cervical cancer rates of the study groups were compared.

Results: The women with multiple HPV subtypes accounted for 24.9% of the study population. Multiple-type HPV infection rates in normal cytology, atypical glandular cells, low-grade squamous intraepithelial lesion (LSIL), atypical squamous cells, cannot exclude HSIL and HSIL were 28.2%, 26.8%, 19.3%, 22.6%, and 21.8%, respectively. Age stratified multiple-type HPV infection rates in under 30 years, 30-49 years and ≥50 years were 27.8%, 24.1%, and 27.3%, respectively. The multiple-type HPV infection rates in LSIL, HSIL, and cancer patients were 31.4%, 19%, and 12.5%, respectively.

Conclusion: Multiple-type HPV infections were statistically less common in HSIL and cancer patients than single type HPV infection. However, multiple type infection rates were remarkable in older HSIL and cervical cancer patients. [J Turk Ger Gynecol Assoc. 2025; 26(2): 90-7]

Keywords: Multiple-type HPV infections, cervical cancer, cytology, histopathologic results

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Introduction

According to GLOBOCAN statistics in 2018, with 570,000 new cases and 311,000 deaths, cervical cancer is the fourth most common gynecological malignancy and human papilloma viruses (HPVs) are the main etiological factor in the development of cervical cancer (1). Analysis of cervical neoplasia lesions show the presence of HPV in of 99.7% of all cervical cancers (2).

Over recent years, pap smear and advanced HPV DNA testing have become more widely used in cervical cancer screening. Routine HPV screening have shown that there are over 200 HPV subtypes, and approximately 40 of them infect the genital tract (3-5). They are classified as high-risk (hr) and low-risk

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(lr) according to oncogenic potential. Infection with HPV is extremely common, but the majority of women infected with HPV do not develop cervical malignancy (6). In addition, the hr types of HPV are generally asymptomatic and, unless tested, women are unaware that they have an HPV infection.

Due to advances in HPV tests in secondary protection, there has been a transition from conventional pap tests, to combined screening or primary HPV-based screening methods (7,8). HPV-based screening systems and more sensitive HPV tests have shown the occurrence of multiple HPV infections and knowledge of these infections was limited (9,10). In addition, it was reported that positive HPV test results, particularly positivity for multiple types of HPV, cause serious fear and anxiety about cervical cancer in the patient group (11).

It is accepted that persistent infections with HPV 16 and HPV 18 types alone are responsible for 70% of cervical cancer (12). On the other hand the rate of infections caused by multiple HPV types is not definitely known. Moreover, their role in cytological abnormalities, cervical preinvasive lesions and cervical cancer is not fully elucidated. Many authors reported possible interactions between types (9,13-15). In contrast, some authors have reported that infections with multiple HPV types occur independently of one another (5,16).

There are still unanswered questions about multiple HPV infections. It is important that clinicians be informed correctly and they enlighten their patients. The aim of this study was to investigate the rate and role of multiple HPV positivity in patients diagnosed with cervical preinvasive lesions and cancer.

Material and Methods

Patients who were referred to our colposcopy clinic from the national screening program and other centers where opportunistic screening was performed, and who underwent colposcopy for the first time between January 2015 and August 2018 were included in the study. All the data of the patients were obtained from Hospital Data Management System and from the colposcopy records. Ethical permission for a retrospective study was granted by the Etlik Zübeyde Hanım Women's Health Education and Research Hospital's Institutional Review Board (approval number: 17, date: 15.11.2019). Patients who had previous colposcopy, conization, a history of hysterectomy, colposcopy due to vulvar diseases, and those who were pregnant were excluded from the study. The HPV tests of patients who were referred from national screening program were made with the Hybrid Capture 2 and genotypings were performed with the CLART kit (Genomica), while the tests of patients referred from opportunistic screening were examined by polymerase chain reaction. Conventional pap test constituted most of the cytological studies. Cytological results were classified according to the Bethesda System. All patients were informed about colposcopy and follow-up procedures and informed consents were obtained. Samples obtained by colposcopic biopsy, loop electrosurgical excision procedure (LEEP) and cold knife conization were evaluated and reported by pathology specialists experienced in Gynecologic Oncology according to the 2011 LAST classification system. For each women the worst cervical histology was defined as the diagnostic end point.

For analysis, the study population was divided into single-type HPV (women with single HPV positivity), and multiple-type HPV (women with multiple HPV positivity). In order to evaluate the effect of single and multiple infections in HPV 16-18 and other types of HPV groups in more detail in the HSIL and cancer patients, HPV subgroups were formed and compared. The term HSIL+ is used hereafter to describe women with HSIL, adenocarcinoma *in situ* or invasive adenocarcinoma, microinvasive or invasive squamous cell carcinoma; carcinoma other than cervix. Four HPV subgroups were formed as follows: group 1: patients with single HPV 16 or 18 positivity; group 2: patients with single other hr (non-HPV 16 and 18) HPV types (HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68); group 3: patients with multiple HPV 16, 18, and other HPV types; and group 4: multiple other hrHPV types Figure 1. The patients were further evaluated by stratifying into three age groups: under 30 years; 30-49 years; and ≥50 years. HSIL and cancer rates in subgroups were compared after age-stratification.

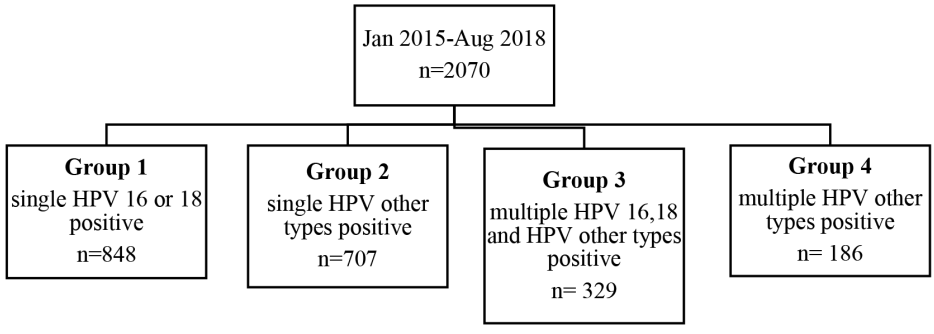

Figure 1. Flowchart of included cases
HPV: Human papillomavirus

Statistical analysis

SPSS, version 17.00 was used for statistical analyses (IBM Inc., Armonk, NY, USA). Quantitative data are expressed as means and standard deviations, and categorical data are described using counts and percentages. Chi-square and Kruskall Wallis tests were used to compare the categorical results of study groups. A $p<0.05$ was accepted statistically significant.

Results

The mean age of the 2070 women included in the study was 44.59±9.24 years. Table 1 summarizes the general characteristics of women entered the study.

The six most common HPV types were HPV16, HPV18, HPV51, HPV31, HPV 52, HPV 45 and the rates were 48.9%, 10.4%, 8.2%, 6.8%, 6.5% and 0.4% respectively. Although it constituted about half of the study group, the type present at the lowest rate in multiple infections was HPV 16.

Multiple HPV rates, based on age groups, are presented in Table 2. Multiple HPV rates were higher in the young (<30 years) and, surprisingly, the over 50 year-old age group, but the difference was not statistically significant ($p>0.05$).

Single and multiple HPV rates based on age-stratified cytology results of the study groups are shown in the Table 3. Multiple HPV rate was 28.2% in patients with normal cytology, 23.5%, 19.3%, 22.6% and 21.7% in atypical squamous cells (ASC) of undetermined significance, low-grade squamous intraepithelial lesion (LSIL), ASC-H, HSIL, respectively. In women with cytology and ≥50 years old, 60% had multiple HPV types, while the rate of multiple HPV infection in patients with normal cytology was 41.7% under 30 years of age and 32.8% in over 50 years of age.

Single and multiple HPV rates based on age-stratified histopathological results of the are shown in Table 4. Based on definitive histopathological results of cervical biopsy, cold knife conization and LEEP interventions, multiple HPV infection rates were 31.4% in LSIL, 32.8% in SIL, 19% in HSIL, and 12.5% in cervical cancer.

Based on age-stratified histopathological results, multiple HPV infection rates in women with LSIL were 33.3% under 30 years of age, and 38.7% in women over 50 years of age. Multiple HPV infection rate was 14% in women over 50 years old with HSIL, and 10% in women over 50 years old with cervical cancer.

Twenty four patients (1.2%) had cervical cancer. When the cervical cancer group was evaluated as adenocarcinoma or squamous cell type, multiple HPV infection rates were 33.5% and 5.6%, respectively. Multiple HPV positivity was detected in 2 of 3 patients (66.7%) diagnosed with non-cervical cancer.

Age-stratified histopathologically HSIL+ rates are presented in Table 5. None of the group under 30 years of age had cancer and only one patient had HSIL so this group was excluded from analysis. HSIL+ rates were significantly higher in group 1 than group 2, group 3 and group 4 in the other age groups ($p<0.001$).

Table 1. Patients characteristics (n=2070)

		n (%)
Age groups	<30	36 (1.7)
	30-49	1,432 (69.2)
	≥50	602 (29.1)
HPV groups	Group 1 (single type)	848 (41)
	Group 2 (single type)	707 (34.2)
	Group 3 (multiple type)	329 (15.9)
	Group 4 (multiple type)	186 (9)
Number of HPV	Single type	1,555 (75.1)
	2 types	354 (17.1)
	3 types	120 (5.8)
	4 types	31 (1.5)
	5 types	6 (0.3)
	6 types	4 (0.2)
Cytology	Normal	468 (22.6)
	Other†	912 (44.1)
	AGC	30 (1.4)
	ASCUS	328 (15.8)
	LSIL	233 (11.3)
	ASCH	53 (2.6)
	HSIL	46 (2.2)
Diagnostic procedure	Cervical biopsy	484 (18.7)
	ECC	365 (17.6)
	Cervical biopsy + ECC	844 (40.8)
	None	375 (18.2)
Intervention	Cold knife conization	266 (12.9)
	LEEP	43 (2.1)
	Other§	83 (4.0)
Histopathology	Benign	1023 (49.4)
	LSIL	287 (13.9)
	SIL	70 (3.4)
	HSIL	284 (13.7)
	Cancer (cervix)	24 (1.2)
	Cancer (non-cervical)	3 (0.1)

AGC: Atypical glandular cells, ASCUS: Atypical squamous cells of undetermined significance, LSIL: Low-grade squamous intraepithelial lesion, ASCH: Atypical squamous cells, cannot exclude high-grade intraepithelial lesion, SIL: Squamous intraepithelial lesion in which low and high-grade squamous intraepithelial lesion cannot be decided, HSIL: High-grade squamous intraepithelial lesion, HPV: Human papillomavirus, Other†: Infection, insufficient cytology, ECC: Endocervical curettage, LEEP: Loop electrosurgical excision procedure, Other§: Patients lost to follow-up after diagnostic procedure. Group 1: Single HPV16/18, group 2: Single HPV other types, group 3: Multiple HPV 16/18 and other HR types, group 4: Multiple other HPV types

Table 2. Multiple HPV rates in age-stratified HPV groups

Age groups	HPV groups		HPV subgroups				
	Single type n (%)	Multiple type n (%)	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	Group 4 n (%)	Total n (%)
<30	26 (72.2)	10 (27.8)	12 (33.3)	14 (38.9)	6 (16.7)	4 (11.1)	36 (100)
30-49	1.091 (76.2)	341 (23.8)	615 (42.9)	476 (33.3)	227 (15.8)	114 (8.0)	1.432 (100)
≥50	438 (72.8)	164 (27.2)	221 (36.8)	217 (36.0)	96 (15.9)	68 (11.3)	602 (100)
Total	1.555 (75.1)	515 (24.9)	848 (41.0)	707 (34.1)	329 (15.9)	186 (9.0)	2.070 (100)

HPV subgroups: Group 1: Single HPV16/18, group 2: Single HPV other types, group 3: Multiple HPV 16/18 and other HR types, group 4: Multiple other HPV types, HPV: Human papillomavirus

Table 3. Age-stratified cytology results of study groups

Cytology	Age groups	HPV groups		HPV subgroups				Total n (%)
		Single type n (%)	Multiple type n (%)	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	Group 4 n (%)	
n	<30	7 (58.3)	5 (41.7)	6 (50.0)	1 (8.3)	3 (25.0)	2 (16.7)	12 (100)
	30-49	241 (74.2)	84 (25.8)	164 (50.5)	77 (23.7)	67 (20.6)	17 (5.2)	325 (100)
	≥50	88 (67.2)	43 (32.8)	51 (38.9)	37 (28.2)	36 (27.5)	7 (5.3)	131 (100)
	Total	336 (71.8)	132 (28.2)	221 (47.2)	115 (24.6)	106 (22.6)	26 (5.6)	**468 (22.6)**
AGC	<30	1 (100)	0 (0.0)	0 (0.0)	1 (100)	0 (0.0)	0 (0.0)	1 (100)
	30-49	19 (79.2)	5 (20.8)	9 (37.5)	10 (41.7)	4 (16.7)	1 (4.2)	24 (100)
	≥50	2 (40.0)	3 (60.0)	2 (40.0)	0 (0.0)	1 (20.0)	2 (40.0)	5 (100)
	Total	22 (73.3)	8 (26.7)	11 (36.7)	11 (36.7	5 (16.7)	3 (10.0)	**30 (1.4)**
ASCUS	<30	8 (66.7)	4 (33.3)	2 (16.7)	6 (50.0)	3 (25.0)	1 (8.3)	12 (100)
	30-49	175 (78.5)	48 (21.5)	70 (31.4)	105 (47.1)	19 (8.5)	29 (13.0)	110 (100)
	≥50	68 (73.1)	25 (26.9)	28 (30.1)	40 (43.0)	8 (8.6)	17 (18.3)	93 (100)
	Total	251 (76.5)	77 (23.5)	100 (30.5)	151 (46.0)	30 (9.1)	47 (14.3)	**328 (15.8)**
LSIL	<30	8 (88.9)	1 (11.1)	2 (22.2)	6 (66.7)	0 (0.0)	1 (11.1)	9 (100)
	30-49	146 (80.2)	36 (19.8)	56 (30.8)	90 (47.5)	15 (8.2)	21 (11.5)	80 (100)
	≥50	34 (81.0)	8 (19.0)	14 (33.3)	20 (47.6)	4 (9.5)	4 (9.5)	42 (100)
	Total	188 (80.7)	45 (19.3)	72 (30.9)	116 (49.8)	19 (8.2)	26 (11.2)	**223 (10.7)**
ASCH	<30	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (100)
	30-49	26 (76.5)	8 (23.5)	20 (58.8)	6 (17.6)	5 (14.7)	3 (8.8)	34 (100)
	≥50	15 (79.0)	4 (21.0)	3 (15.8)	12 (63.2)	1 (5.3)	3 (15.8)	19 (100)
	Total	41 (77.4)	12 (22.6)	23 (43.4)	18 (34.0)	6 (11.3)	6 (11.3)	53 (2.6)
HSIL	<30	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (100)
	30-49	25 (73.5)	9 (26.5)	22 (64.7)	3 (8.8)	4 (11.8)	5 (14.7)	34 (100)
	≥50	11 (91.7)	1 (8.3)	6 (50.0)	5 (41.7)	1 (8.3)	0 (0.0)	12 (100)
	Total	36 (78.3)	10 (21.7)	28 (60.9)	8 (17.4)	5 (10.9)	5 (10.9)	**46 (2.2)**
Other	<30	2 (100)	0 (0.0)	2 (100)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100)
	30-49	459 (75.2)	151 (24.8)	274 (44.9)	185 (30.3)	113 (18.5)	38 (6.2)	610 (100)
	≥50	220 (73.3)	80 (26.7)	117 (39.0)	103 (34.5)	45 (15.0)	35 (11.7)	300 (100)
	Total	681 (74.5)	231 (25.3)	393 (43.1)	288 (31.6)	158 (17.3)	73 (8.0)	912 (44.1)
Total		1,555 (75.1)	515 (24.9)	848 (40.96)	707 (34.15)	329 (15.9)	186 (8.98)	**2,070 (100)**

N: Normal, AGC: Atypical glandular cells, ASCUS: Atypical squamous cells of undetermined significance, LSIL: Low-grade squamous intraepithelial lesion, ASCH: Atypical squamous cells, cannot exclude high-grade intraepithelal lesion, HSIL: High-grade squamous intraepithelial lesion, HPV: Human papillomavirus, Other: Infection, insufficient cytology, group 1: Single HPV16/18, group 2: Single HPV other types, group 3: Multiple HPV 16/18 and other HR types, group 4: Multiple other HPV types

HSIL+ rates in group 2 and group 4 were not significant being p=0.763 in <50 year-olds and p=0.317 in ≥50 year-olds. Single HPV types were more prevalent in HSIL+ patients. In older patients HSIL+ rates in group 2 and in group 3 were not different.

HPV type distribution in cases with HSIL and cancer are presented in Table 6. While the rate of multiple HPV was 28.1% in the older age group (age ≥50 years), in younger women (30-49 years age group) multiple HPV types were the causal agent in 19% of those with HSIL.

Table 4. Age-stratified histopathologic findings of study groups

Histopathology	Age groups	HPV groups		HPV subgroups				Total n (%)
		Single type n (%)	Multiple type n (%)	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	Group 4 n (%)	
Benign	<30	6 (60.0)	4 (40.0)	3 (30.0)	3 (30.0)	3 (30.0)	1 (10.0)	10 (100)
	30-49	493 (75.8)	157 (24.2)	253 (38.9)	240 (36.9)	105 (16.2)	52 (8.0)	650 (100)
	≥50	259 (71.3)	104 (28.7)	125 (34.4)	134 (36.9)	58 (16.0)	46 (12.7)	363(100)
	Total	758 (74.1)	265 (25.9)	381 (37.2)	377 (36.9)	166 (16.2)	99 (9.7)	**102 3 (49.4)**
LSIL	<30	6 (66.7)	3 (33.3)	1 (11.1)	5 (55.6)	0 (0.0)	3 (33.3)	9 (100)
	30-49	161 (70.3)	68 (29.7)	86 (37.6)	75 (32.8)	42 (18.3)	26 (11.4)	229 (100)
	≥50	30 (61.2)	19 (38.8)	17 (34.7)	13 (26.5)	11 (22.4)	8 (16.3)	49 (100)
	Total	197 (68.6)	90 (31.4)	104 (36.2)	93 (32.4)	53 (18.5)	37 (12.9)	**287 (13.9)**
SIL	<30	2 (100)	0 (0.0)	1 (50.0)	1 (50,0)	0 (0.0)	0 (0.0)	2 (100)
	30-49	32 (65.3)	17 (34.4)	26 (53.1)	6 (12.2)	13 (26.5)	4 (8.2)	49 (100)
	≥50	13 (68.4)	6 (31.6)	9 (47.4)	4 (21.1)	5 (26.3)	1 (5.3)	19 (100)
	Total	47 (67.1)	23 (32.9)	36 (51.4)	11 (15.7)	18 (25.7)	5 (7.1)	**70 (3.4)**
HSIL	<30	1 (100)	0 (0.0)	1 (100)	0 (0.0)	0 (0.0)	0 (0,0)	1 (100)
	30-49	186 (79.8)	47 (20.2)	150 (64.4)	36 (15.5)	39 (16.7)	8 (3.4)	233 (100)
	≥50	43 (86.0)	29 (24.6)	29 (58.0)	14 (28.0)	5 (10.0)	2 (4.0)	50 (100)
	Total	230 (81.0)	54 (19.0)	180 (63.4)	50 (17.6)	44 (15.5)	10 (3.5)	**284 (13.7)**
Cevical cancer	<30	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (100)
	30-49	12 (92.3)	1 (7.7)	10 (76.9)	2 (15.4)	0 (0.0)	1 (7.7)	13 (100)
	≥50	9 (81.8)	2 (18.2)	9 (81.8)	0 (0.0)	2 (18.2)	0 (0.0)	11 (100)
	Total	21 (87.5)	3 (12.5)	19 (79.2)	2 (8.3)	2 (8.3)	1 (4.2)	**24 (1.2)**
Non-cervical cancer	<30	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (100)
	30-49	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (100)
	≥50	1 (33.3)	2 (66.7)	0 (0.0)	1 (33.3)	1 (33.3)	1 (33.3)	3 (100)
	Total	1 (33.3)	2 (66.7)	0 (0.0)	1 (33.3)	1 (33.3)	1 (33.3)	**3 (0.1)**
Total		1,254 (74.2)	437 (25.8)	720 (42.6)	534 (31.6)	284 (16.8)	153 (9.0)	1,691 (100)

Benign, histopathologic results such as cervicitis, polyps, microglanduler hyperplasia. LSIL: Low-grade squamous intraepithelial lesion, SIL: Squamous intraepithelial lesion grade cannot decided low or high, HSIL: High-grade squamous intraepithelial lesion cervical cancer, SCC: Microinvasive or invasive squamous cell carcinoma, HPV: Human papillomavirus, Non-cervical cancer, carcinoma other than cervix, group 1: Single HPV16/18, group 2: Single HPV other types, group 3: Multiple HPV 16/18 and other HR types, group 4: Multiple other HPV types

Table 5. Age-stratified HSIL+ rates of HPV subgroups

HPV subgroups	Age groups	30-49		≥50	
		HSIL+ n (%)	p	HSIL+ n (%)	p
Group 1		161/627 (25.7)	<0.001	38/221 (17.2)	<0.001
Group 2*[a]		38/490 (7.8)		15/217 (6.9)	
Group 3[a]		39/233 (16.7)		8/96 (8.3)	
Group 4*		9/118 (7.6)		3/68 (4.4)	

HSIL+: High-grade squamous intraepithelial lesion, adenocarcinoma *in situ* or invasive adenocarcinoma, microinvasive or invasive squamous cell carcinoma; carcinoma other than cervix, Chi-square tests: HSIL+ rates were statistically significant higher in group 1 than group 2, group 3, and group 4 in both age groups (p<0.001). *The difference of HSIL+ rates between group 2 and group 4 was not statistically significant in both age groups (p>0.05). [a]HSIL+ rates in group 2 versus group 3 were not statistically significant in age ≥50 (p=0.657), HPV: Human papillomavirus

Table 6. Age stratified HPV type distribution in HSIL+

HSIL+ age groups, years	HPV groups		HPV subgroups				Total n (%)
	Single type n (%)	Multiple type n (%)	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	Group 4 n (%)	
30-49	200 (81.0)	47 (19.0)	161 (65.2)	38 (15.4)	39 (15.8)	9 (3.6)	247 (100)
≥50	46 (71.9)	18 (28.1)	38 (59.4)	15 (23.4)	8 (12.5)	3 (4.7)	64 (100)
Total	246 (79.1)	65 (20.9)	199 (64.0)	53 (17.0)	47 (15.1)	12 (3.9)	311 (100)

HSIL+: High-grade squamous intraepithelial lesion, adenocarcinoma *in situ* or invasive adenocarcinoma, microinvasive or invasive squamous cell carcinoma; carcinoma other than cervix, Group 1: Single HPV16/18, Group 2: Single HPV other types, Group 3: Multiple HPV 16/18 and other HR types, Group 4: Multiple other HPV types, HPV: Human papillomavirus

Multiple HPV infections were detected in only three of the 24 cervical cancer cases (13%) and 18 (78%) had HPV 16 infection alone. Single HPV 18 infection was detected in one patient (4%) and single HPV of another type was detected in two patients (HPV 56, HPV 59). When the cytology results of the patients diagnosed with cancer were reviewed, it was reported as HSIL in three patients, ASC, cannot exclude high-grade intraepithelal lesion in one patient, and suspicious cytology in two patients. Furthermore, 14 (60%) of the patients with cancer were over 50 years old.

Discussion

Multiple HPV positivity is becoming more frequently detected and reported due to improvements in HPV testing methods and widespread use of HPV testing in cervical cancer screening (4,10,17). Identifying the role of multiple-type HPV infections in cervical preinvasive disease and cervical cancer is important for improving screening, follow-up strategies and HPV vaccine policy (15).

In the literature, multiple HPV positivity has been examined from different aspects including the prevalence, age distribution, cytological relations, histopathological correlations, and treatment response (4,5,9,14,15,18-29). Initial studies into multiple HPV are usually related to prevalence, and in the majority of the studies lr and hr types have been studied together. The rate varies widely from 20-100% (4,14,18-20). In the current study, only hrHPV types were studied and the rate of multiple-type HPV was 24.9%. All these studies show that multiple-type HPV infections are a common phenomena in sexually active women, infection rate varies according to the sensitivity of the test used and the age distribution of the group screened (24). However, knowing the multiple HPV rate alone is not sufficient for optimal management of women infected with HPV. In Türkiye the prevalence of hrHPV was reported as 3.5% and the commonest type was HPV 16 with 20.5% of HPV positive women (0.7% of all women). It was followed by types 51, 31, 52, 18 with rates of 10.5%, 8.3%, 7.8%, and 4.5%, respectively. No data related to multiple HPV infection were presented (30).

It is noted in many publications that multiple HPV positivity is more common in young women and in the older postmenopausal group. Impaired immune system and multiple sexual partners have been reported as the main factors (5,21). Safaeian and Rodriguez (20) reported that the distribution of concurrent infections varied by age and cervical abnormality, being highest in persons with abnormal lesions. Yang et al. (9) reported that multiple HPV infections were more common among young women with low-grade cytology and also among older women. Aro et al. (24) reported that multiple HPV types were most common in women <30 years of age. Resende et al. (23) also reported the prevalence of multiple type infections followed a bimodal distribution, peaking in women younger than 29 years and again in those aged 50 to 59 in Brazilian women.

Türkiye's national cervical cancer screening program covers women aged 30-65 years (30). In the present study, when HPV-positive patients were examined by age group, the prevalence of multiple HPV positivity in the below 30 years and above 50 years groups were found to be non-significantly higher (27.8 and 27.2%) than in the 30-49 years-old age group.

Many studies have reported that multiple HPV positivity is higher in women with abnormal cytology (5,9,15,20,25). Due to the low sensitivity of cervical cytology, its relationship with multiple HPV infections cannot be clearly demonstrated. Insufficient cytology rates are frequently encountered, especially when using the conventional pap smear test. Based on cytology reports, the rate of multiple HPV was 28.2% in those with normal cytology, 19.3% in LSIL, and 21.5% in HSIL cytology in the present study. Of note, 44.1% of cytology results were reported as "infection" or "insufficient".

The relationship between multiple HPV infection and histopathological results is the most important factor for selecting optimal patient management. However, they are conflicting results. Some publications related to multiple HPV infections with histological results show an increase in high-grade cervical preinvasive disease, while others do not. Carrillo-García et al. (25) reported that their data suggested that the presence of more than one hrHPV type increased the

risk of developing high-grade cervical lesions and invasive cervical cancer. Chaturvedi et al. (21) also reported that multiple oncogenic types of α9 species increased the risk of both cervical intraepithelial neoplasia 2 (CIN2) and HSIL. Akış et al. (22) reported that the multiple HPV group had a high rate of CIN lesions. Senapati et al. (19) reported that women infected with multiple genotypes with phylogenetically related clad had the higher risk of cervical carcinoma as compared to the population infected with phylogenetically unrelated clad. Spinillo et al. (26) reported among women with cervical cytological abnormalities that infection by multiple hrHPVs increased the risk of CIN3+ in both HPV16-positive and HPV16-negative women. De Brot et al. (6) reported that HPV coinfections was present in the majority of HSIL cases.

In contrast, Aguilar-Lemarroy et al. (27) reported that, when considering HPV-positive samples only, coinfections occurred most often in controls (63%) and were less frequent in those with cervical cancer (26%). Wu et al. (28) reported HPV16/18 co-infection with other hrHPVs to be a common phenomenon and they also found that HPV16 co-infected with other hrHPVs appeared to have a lower associated risk of CIN3+ in ≥30 year-old women. In serological studies, a tendency for antagonistic interactions between HPV16 and HPV18 were demonstrated. Seropositivity for HPV18 reduces the risk of HPV16-related cervical cancer (31).

In the present study, only 2.46% of patients with HSIL had HPV 16/18 coexistence, but no HPV 16/18 positivity was found in patients diagnosed with cervical cancer. The results of this study also showed that multiple type HPV rates were less common in HSIL and cancer cases.

Study Limitations

The study has some limitations. This study was cross-sectional. Follow-up results were not available. Furthermore, solely results related to hrHPV types are presented. The study center is a referral center and so the study population may introduce some selection bias.

The strengths of the study include an estimated large population. This is because hrHPV positivity in Türkiye was reported as 3.5%, and of that 20% was HPV16 (0.7%) so that the number of patients participating in this study roughly represents about 150,000 Turkish women. Moreover, we present the histological data of multiple hrHPV positive patients, as well as prevalence and cytological data. Our hospital provides services for gynecological cancers and our pathologists are highly experienced in this field. Also experienced gyneco-oncologists work in our colposcopy outpatient clinic. In addition, our colposcopy clinic is one of the colposcopy reference centers of the national HPV based screening system.

Conclusion

In the present study multiple-type HPV infections were less common than single-type infections in high-grade cervical lesions and cervical cancer. Our results suggest that multiple HPV positivity may be related to shorter duration of infection and this may be the main reason for low HSIL+ rates. However, the rate of multiple type infections in HSIL and cervical cancer patients in women older than 50 years was remarkable, although not statistically significantly different from the other age group (28.1%). However, the age of the women should be taken into account in the triage of Turkish women and possibly in other populations too, but this suggestion requires data from other populations before widespread implementation.

To gain more insights into the natural history and dynamics of multiple HPV infections, more sensitive assays and longitudinal studies with long-enough follow-up periods are necessary. Comprehensive and long follow-up results of national HPV screening programs will be particularly important because of the regional HPV distribution. In the light of these results, more efficient strategies will need to be developed to prevent preinvasive disease and cervical cancer.

Ethic

Ethics Committee Approval: *Ethical permission for a retrospective study was granted by the Etlik Zübeyde Hanım Women's Health Education and Research Hospital's Institutional Review Board (approval number: 17, date: 15.11.2019).*

Informed Consent: *All patients were informed about colposcopy and follow-up procedures and informed consents were obtained.*

Footnotes

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

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Evaluation of the efficacy of mini-sling in the treatment of stress urinary incontinence through patient-reported outcomes and transperineal ultrasonography

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Abstract

Objective: Single-incision slings, such as Contasure-Needleless® (C-NDL), were developed to improve surgical treatment success in stress urinary incontinence (SUI). However, more evidence is needed to describe the outcomes of mini-sling procedures as an alternative to classical mid-urethral slings. The aim was to evaluate the short-term outcomes of the mini-sling procedure using C-NDL in the surgical treatment of SUI patients.

Material and Methods: This was a single-center, prospective study including 24 patients with SUI who underwent C-NDL. Michigan Incontinence Severity Index (M-ISI) questionnaire, the Female Sexual Function Index, and the Patient Global Impression of Improvement (PGI-I) questionnaire were applied, as well as trans-perineal ultrasound evaluations at baseline, one month and six months postoperatively.

Results: The PGI-I index showed that 54.17% of participants described their post-operative recovery as "very much better" and 29.17% as "much better". Significant improvements were observed in all SUI and M-ISI-related results. No significant differences were detected in terms of FSFI. Complications were reported as *de novo* urgency in 4 (16.67%) patients, mesh erosion in 2 (8.33%) patients, and pelvic pain and infection in 1 patient each (4.17%). The mean distance of the mini-sling mesh to the urethra was found to be 5.51±2.3 mm at one month and 4.69±1.85 mm at six months after surgery ($p=0.006$). The mean urethral rotation angle was decreased following surgery ($p<0.001$). No significant differences were observed between patients with and without cure regarding any of the examined variables.

Conclusion: For SUI treatment, the C-NDL procedure is a safe and effective method with few complications and high subjective cure rates on short-term follow-up (6 months). [J Turk Ger Gynecol Assoc. 2025; 26(2): 98-108]

Keywords: Urinary incontinence, stress, suburethral slings, ultrasonography, postoperative complications, patient reported outcome measures

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Introduction

Urinary incontinence (UI) is characterized by involuntary urinary leakage that negatively affects quality of life, including social, emotional, sexual, and professional domains (1). Its prevalence varies widely from 5% to 70% depending on the definition used, and risk factors include advanced age, female sex, parity, race, menopausal status, smoking, constipation, obesity and previous gynecological surgery (2). According to a systematic review, the prevalence of urinary incontinence among Turkish women ranges from 16.4% to 49.7% (3). Patients are often reluctant to seek treatment, with reasons such as the

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perceiving UI as a part of natural aging, hesitation to report complaints, lack of information about treatment methods, fear of surgery, and belief that all kinds of treatment are useless. Therefore, risk factors and complaints should be evaluated in detail to determine the need for treatment. Moreover, therapeutic options should be evaluated comprehensively and surgical interventions should be as non-invasive as possible while restoring quality of life without compromising efficacy.

Stress UI (SUI) is particularly prevalent in middle-aged and postmenopausal women, which is related to abrupt elevation of abdominal pressure (defeating closure pressure), exemplified by incontinence occurring during coughing, laughing, heavy lifting, and exercise (4). Although conservative treatments, such as electrical simulation, laser therapy, urethral bulking, and pelvic muscle training, with or without pharmacotherapy, are used with certain levels of success in patients with SUI, the surgical approaches have advanced rapidly (5). Tension-free vaginal tape (TVT) and transobturator tape (TOT) are common, effective and relatively safe procedures with success rates of 80% to 90% but these surgeries pose a risk for major complications associated with needle insertion through the abdomen or groin, including vascular injury and chronic pain (6). Over the years, third-generation, minimally invasive slings with shorter mesh length single-incision slings (SIS) have emerged, reducing complications and preventing blind manipulation of trocars in the obturator canal and Retzius space (7). However, clinical studies are needed to obtain more evidence regarding the efficacy of mini-slings as an alternative to classical mid-urethral slings.

In this study the short-term effects of the mini-sling procedure using the Contasure-Needleless® (C-NDL) device (Neomedic International SL, Barcelona, Spain) were evaluated in patients with SUI by performing ultrasonographic examinations and validated questionnaires over a 6-months follow-up period.

Material and Methods

Study design

This was a single-center, prospective study conducted between March 2019 and June 2019 in a tertiary center. All patients with clinically proven SUI who were candidates for SI, mid-urethral sling procedure with C-NDL were eligible for study inclusion.

The diagnosis of SUI was made via symptomatic assessment and demonstration of cough test positivity in the supine and standing positions with a saline-filled bladder (300 mL). Participants with diabetes mellitus, major neurological disease or stroke, previous anti-incontinence surgery, acute infection, previous or concomitant pelvic reconstructive surgery, and > Stage I pelvic organ prolapse (POP) assessed by the POP Quantification (POP- Q) system were excluded from the study.

All research procedures conformed to the Declaration of Helsinki and were approved by the Local Research Ethics Committee of the University of Health Sciences Türkiye, Fatih Sultan Mehmet Training and Research Hospital (approval number: 2019/19, date: 14.03.2019). Written and signed informed consent forms were obtained from each study participant prior to enrollment. A comprehensive preoperative evaluation was performed, including medical history, gynecological and ultrasound examinations, urinalysis, and validated condition-specific questionnaires. Baseline data including age, body mass index (BMI), parity, type of birth delivery, history of macrosomic neonate delivery, menopausal status, sexual life, history of gynecological surgery, smoking, concomitant diseases (diabetes mellitus, hypertension, goiter, chronic obstructive pulmonary disease, chronic constipation, urgency), and duration and treatments for incontinence were obtained from patient files. No urodynamic testing was performed on patients before the procedures.

In line with NICE Guideline NG123 (2019) Recommendation 1.4.1-which states that preoperative urodynamic testing is not required in women with uncomplicated, clinically diagnosed SUI, urodynamic studies were omitted in our cohort, and diagnosis relied solely on a positive cough stress test.

Measures

The Turkish-language validated version of the Michigan Incontinence Severity Index (M-ISI) questionnaire, the Hospital Anxiety and Depression Scale (HADS), and the Female Sexual Function Index questionnaire were applied to all participants before and after the mini-sling procedure (8-10). All these questionnaires and the the Patient Global Impression of Improvement (PGI-I) were the validated Turkish-language versions and were administered via face-to-face interview by a physician who was not involved in the surgical procedures and was blinded to study design, rather than being self-completed by participants.

Quality of life associated with incontinence was examined with the M-ISI (11). M-ISI is a Likert-type scale that includes a total of 10 questions, the first three questions examine SUI, the second three questions examine UUI, the 7th and 8th questions examine pad use, and the last two questions examine how much this situation bothers the patient. Responses to each item ranged from 0 to 4; higher values represent more symptoms and more discomfort. Minimal difference values for significance were determined as 4 points for total M-ISI, 2 points for SUI, 2 points for UUI, and 1 point for the use of pads (11).

The FSFI is a 19-item, self-reported questionnaire that provides scores on six subsections, including sexual desire, arousal, lubrication, orgasm, satisfaction and pain, which can be used with women who have had sexual intercourse in the last month (12). The subdomain scores range between 0 and 5, and the

total score was obtained by multiplying the scores obtained from the domains with their own coefficients. The cut-off point for distinguishing sexual dysfunction from normal sexual function was accepted as a total score of 26.55.

The HADS consists of 14 items (4-point Likert) that score anxiety (n=7) and depression (n=7) (13), resulting in subscale values ranging from 0 to 21 points. Anxiety cut-off was 10 and depression cut-off was 7.

In addition, the PGI-I was used as a subjective measure to assess mini-sling success (14). This is a simple, direct and easy-to-use scale that can be intuitively understood by both physicians and patients, and consists of a single question comparing postoperative status with baseline. Responses categorize patients into seven groups ranging from "very much better" to "very much worse". In addition, a 3-item Likert scale was used to describe subjective overall satisfaction. According to the scale, responses were divided into three groups: a response of 3 indicated "cured, very satisfied, no UI"; 2 indicated "satisfied, less UI, an improvement in the condition compared to before"; and 1 was for "not satisfied, condition did not change or worsened compared to pre-operative period".

Complete cure was defined as both (1) objective resolution (negative postoperative cough stress test) and (2) subjective resolution (no leakage episodes, no pad use, and patient-reported "very satisfied" on the 3-point Likert scale or "very much better" on the PGI-I questionnaire.

Mini-sling procedure

All mini-sling procedures were performed under general anesthesia, based on previously reported approaches (15,16). Briefly, the bladder was emptied with a Foley catheter while patients were in the dorsal lithotomy position. The SI needleless mini-sling mesh (C-NDL) used during the operation has a macropore monofilament mesh structure made of polypropylene material, with dimensions of 114 × 12 mm. The anterior vaginal wall was opened with a longitudinal incision (15-20 mm) at the mid-urethral level. From this incision, a passage/tunnel was opened bilaterally (45°, towards 10 and 2 o'clock) with dissecting scissors until the ischiopubic ramus was felt in the paraurethral area. The T-pocket positioning of the mesh was compressed by folding it concavely using Kelly clamps. The mesh (held with a clamp) was advanced through the tunnel. The fascia of the internal obturator muscle was perforated in a controlled manner. Then, the mouth of the clamp was opened, allowing the mesh T-pocket to be placed, and the clamp was withdrawn in a semi-closed form. Then these processes were repeated contralaterally. The positioning and the tension of the T-pockets were checked by employing a centering suture, which was then cut and removed. The vaginal incision was closed using 2/0 absorbable sutures. Any perioperative complications were monitored; none occurred. Postoperative urinary retention was absent, and discharge was on day 1 for all subjects.

Follow-up

Scheduled at 1 and 6 months, each visit involved pelvic examination, cough stress test, trans-perineal ultrasound, and questionnaires. All signs and symptoms were categorized by the examining surgeons according to the International Continence Society/International Urogynecological Association Complications Classification Code guidelines. No patients underwent additional surgical interventions or routine intraoperative cystoscopy.

A 6-month follow-up was chosen to capture early postoperative efficacy and safety outcomes. As reported in previous meta-analyses, the majority of failures and complications of SI mini-slings typically manifest within this timeframe (17,18).

Ultrasound examinations

Trans-perineal ultrasound (preoperative and postoperative 1 and 6 months) was conducted at rest and at maximum Valsalva, by a single investigator who was not involved in the surgical treatment process. The urinary bladder, urethra, pubic symphysis and sling-associated parameters were evaluated in the mid-sagittal plane. Bladder neck descent, proximal urethral rotation angle, retrovesical angle, and hiatal opening were measured and recorded by Dietz's standard method using 3D convex probes (Mindray DC-8 PRO ultrasound device; Shenzhen, China) (19). The sling was identified as a hyperechoic structure under the urethra. Minimal sling-to-symphysis pubis distance was measured and recorded during the Valsalva maneuver. Sling-urethra distance was determined based on the shortest distance between the sling and the hypoechoic urethra. In order to calculate the urethra-relative sling position, bladder neck-to-center-sling distance was divided by the length of the urethra and defined as a percentage. Proximal urethral rotation angle was described as the angle between the resting and Valsalva states of the proximal urethra.

Statistical analysis

SPSS, version 25.0, was used for data collection and analyses (IBM Inc., Armonk, NY, USA). All p values less than 0.05 were accepted as being significant. Descriptive statistics of continuous data are summarized using mean ± standard deviation for normally distributed data or median (25-75 percentiles) for non-normal distribution. Frequency and percentage were described to summarize categorical variables. Normal distribution assumption was checked using the Shapiro-Wilk test. Normally distributed preoperative and postoperative measurements were analyzed using the paired

t-test or repeated measures analysis of variance (ANOVA) depending on the number of measurements. Non-normally distributed preoperative and postoperative measurements were analyzed using the Wilcoxon signed ranks test or Friedman's ANOVA by ranks, again depending on the number of measurements. Bonferroni correction was used for all pairwise comparisons. Between groups analysis of continuous variables was performed using the Student's t-test or the Mann-Whitney U test, depending on parametricity. Between groups analyses of categorical variables were performed using Fisher's exact test or its Fisher-Freeman-Halton extension.

Results

Thirty patients admitted in the study period were evaluated for eligibility as candidates for surgical treatment. Three were excluded due to missing questionnaires or treatment refusal. Participants who did not attend their follow-up appointments were considered lost to follow-up (n=2). One participant with inaccurate questionnaire responses was excluded. Thus, twenty-four women were included in analyses. Mean age was 45.04±7.37 years. The mean BMI value was 30.33±4.97 kg/m^2, and 37.5% of patients had obesity. Almost a third (29.17%) of women were postmenopausal but none had received hormone replacement therapy. While 70.83% of women had given birth vaginally, 29.17% had undergone Cesarean delivery. The median duration of incontinence complaints was 4 (1.5-5.5) years. According to the HADS score test, the depression subgroup result was found to be 8.04±4.66, while the anxiety subgroup result was 8.96±4.96. In terms of ultrasonography findings, the mean diameter of hiatal opening was 56.43±6.9 mm, urethral length was 31.52±4.12 mm, and bladder neck descent was 15.9±6.46 mm. The mean retrovesical angle was 140.71±23.79°. (Table 1)

The mean distance of the mini-sling mesh to the urethra was 5.51±2.3 mm at the 1st month and 4.69±1.85 mm iat the 6th month after surgery (p=0.006). No difference was detected in the sling position relative to the urethra and the sling-symphysis pubis distance between the 1st and 6th months after surgery (p=0.361 and p=0.547, respectively). At the 6th month after procedure, symmetrical mesh arms (sling material) were observed in 19 (82.61%) subjects, and the sling demonstrated a straight shape in 17 (73.91%) subjects. Complications were reported as *de novo* urgency in 4 (16.67%) patients, mesh erosion in 2 (8.33%), pelvic pain in 1 (4.17%), and infection in 1 (4.17%). According to the PGI-I, 54.17% of the participants described their postoperative recovery as "very much better" and 29.17% as "much better". According to the 3-item Likert scale describing subjective overall satisfaction, 14 (58.33%) patients responded with "improved, very satisfied, no incontinence" (Table 2).

While the mean preoperative total FSFI score of sexually active patients (n=18) was 20.17±8.81, the postoperative total mean FSFI score was 20.32±9.1 (p=0.833). No differences were detected in any of the FSFI subdimensions (all, p>0.05) (Table 3). The median total severity M-ISI score was 18 (13.5-26.5) at baseline, 4 (2-8) at the 1st postoperative month, and 5 (1.5-10.5) at the 6th postoperative month (p<0.001). Significant improvements in postoperative M-ISI scores were detected (all, p<0.001) (Table 4). Anatomical measurements showed that the

Table 1. Demographics and clinical characteristics of patients in the preoperative period

Variables	Results
Age, years	45.04±7.37
Body mass index, kg/m^2	30.33 4.97
Parity, n	3 (2-3)
History of vaginal delivery, n	17 (70.83%)
Giving birth to macrosomic infant, n	2 (8.33%)
Menopausal status	
Premenopausal, n	17 (70.83%)
Postmenopausal, n	7 (29.17%)
Sexual life	
Passive, n	6 (25.00%)
Active, n	18 (75.00%)
Gynecological operation	14 (58.33%)
C/S, n	13 (54.17%)
TAH, n	1 (4.17%)
Smoking, n	8 (33.33%)
Diabetes mellitus, n	2 (8.33%)
Hypertension, n	6 (25.00%)
Goiter, n	3 (12.50%)
COPD, n	1 (4.17%)
Chronic constipation, n	2 (8.33%)
Duration of incontinence, years	4 (1.5 - 5.5)
HADS score	
Depression	8.04±4.66
Anxiety	8.96±4.96
Urethral funneling, n	8 (33.33%)
Hiatal opening, mm	56.43±6.90
Retrovesical angle, °	140.71±23.79
Bladder neck descent, mm	15.90±6.46
Urethral length, mm	31.52±4.12

C/S: Cesarean section, TAH: Total abdominal hysterectomy, COPD: Chronic obstructive pulmonary disease, HADS: Hospital Anxiety and Depression Scale. Descriptive statistics are presented using mean ± standard deviation for normally distributed continuous variables, median (25th percentile-75th percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables

Table 2. Sling-related measurements and outcomes of the patients

Variables	Results
Sling-bladder neck, mm	22.20±3.53
Relative sling position, %	
1st month	70.64±8.56
6th month	71.79±7.24
p	0.361†
Sling-symphysis distance, mm	
1st month	20.36±3.30
6th month	20.68±3.35
p	0.547†
Sling-urethra distance, mm	
1st month	5.51±2.30
6th month	4.69±1.85
p	0.006†
Sling status	
Symmetrical, n	19 (82.61%)
Asymmetrical, n	4 (17.39%)
Sling shape	
Straight line, n	17 (73.91%)
Curved, n	1 (4.35%)
Folded, "V" shape, n	5 (21.74%)
Complication	8 (33.33%)
De novo urgency, n	4 (16.67%)
Mesh erosion, n	2 (8.33%)
Pelvic pain, n	1 (4.17%)
Infection, n	1 (4.17%)
PGI-I	
Very much better, n	13 (54.17%)
Much better, n	7 (29.17%)
A little better, n	1 (4.17%)
No change, n	2 (8.33%)
A little worse, n	0 (0.00%)
Much worse, n	1 (4.17%)
Very much worse, n	0 (0.00%)
Outcome	
Cured (no leakage), n	14 (58.33%)
Improved (minimal leakage), n	7 (29.17%)
No change or worse, n	3 (12.50%)

PGI-I: Patient Global Impression of Improvement. Descriptive statistics are presented using mean ± standard deviation for normally distributed continuous variables and frequency (percentage) for categorical variables. †Paired t test

mean urethral rotation angle was 71.75±11.38° before surgery, and it decreased to 42.42±10.29° in the 1st month after surgery, and to 37.39±12.90° in the 6th month after surgery (p<0.001). Bladder wall thickness was similar in the preoperative and postoperative periods (p=0.977) (Table 4).

Finally, when those with and without cure after treatment were analyzed (Tables 5, 6), all parameters were found to be similar in these subsets (all, p>0.05).

Discussion

The aim of this study was to assess short-term mini-sling surgery outcomes by comparing pre- and post-operative transperineal ultrasonography results and subjective success rates in SUI patients. Scores assessing quality of life, including the PGI-I, M-ISI, and 3-item Likert scale, showed measurable and patient-reported improvements with the mini-sling surgery. As such, our results demonstrate high satisfaction over short-term follow-up and few complications, suggesting that C-NDL is a reliable management strategy for SUI. Notably, we did not observe any significant differences in terms of demographic and clinical characteristics, ultrasonographic examination results, and mini-sling-related parameters between patients with and without surgical success.

Mini-sling procedures were introduced in 2006 to reduce postoperative complications and improve quality of life (shorter mesh, single incision), but efficacy is still unclear due to limited data and different types of SIS procedures being performed throughout the world. The main indicator used to evaluate the effectiveness of mini-sling procedures is cure rate (subjective and objective). A meta-analysis in 2011 compared TVT-Secure, Mini-Arc, and Ophira to classical midurethral slings. The data showed lower cure rates with the newer approaches (17). In a later meta-analysis performed in 2014, success rates and quality of life scores were similar with mini slings compared to classical midurethral slings after a follow-up of 12-36 months (18). Importantly, these authors observed similar rates of lower urinary tract injury, postoperative micturition, vaginal mesh erosion, and *de novo* urgency, with the exception of TVT-Secure. Luo et al, compared C-NDL and TVT/TOT-O for female patients with SUI in a meta-analysis and found that C-NDL was equally effective in terms of subjective and objective recovery rate, and had advantages of shorter operative times, fewer complications, with the exception of groin pain, and less postoperative pain (20). Our data from mini-sling procedures show an improvement in subjective cure rates and patient satisfaction. The PGI-I revealed that 83% of our patients described their postoperative recovery as "much better" or "very much better". Similarly, Dogan et al. (16) described a cure rate of 89.9% with C-NDL in a 24-month follow-up of 80 SUI patients. Naumann et al. (21) reported that 86.3% of patients

Table 3. Pre- and post-operative FSFI scores of the patients

FSFI score (n=18)	Baseline	6th month	p
Desire	2.90±1.44	3.17±1.36	0.415†
Arousal	3.22±1.62	3.12±1.79	0.728†
Lubrication	3.6 (3.3-4.5)	3.9 (3.0-4.5)	0.207‡
Orgasm	4.0 (2.8-5.2)	4.0 (2.4-5.2)	0.573‡
Satisfaction	3.69±1.47	3.71±1.62	0.917†
Pain	3.24±2.09	2.96±1.73	0.508†
Total	20.17±8.82	20.32±9.11	0.833†

FSFI: Female Sexual Function Index. Descriptive statistics were presented using mean ± standard deviation for normally distributed continuous variables, median (25th percentile-75th percentile) for non-normally distributed continuous variables. †Paired t test, ‡Wilcoxon signed ranks test

Table 4. Michigan Incontinence Symptom Index scores and anatomical measurements of the patients

M-ISI score	Baseline	1st month	6th month	p
SUI	7 (5-10)	0 (0-2)*	0 (0-3)*	<0.001‡
UUI	7.5 (4-10)	2 (0-4)*	3 (0-4.5)*	<0.001‡
Pad usage	4.5 (3-6)	2 (0.5-2)*	2 (0.5-3)*	<0.001‡
Bother	5.5 (4-6.5)	0 (0-2)*	0 (0-2)*	<0.001‡
Total severity	18 (13.5-26.5)	4 (2-8)*	5 (1.5-10.5)*	<0.001‡
Bladder wall thickness, mm	5.47±0.69	5.45±0.75	5.49±1.11	0.977†
Urethral rotation angle	71.75±11.38	42.42±10.30*	37.38±12.90*	<0.001†

M-ISI: Michigan Incontinence Symptom Index, SUI: Stress urinary incontinence, UUI: Urgency urinary incontinence. Descriptive statistics were presented using mean ± standard deviation for normally distributed continuous variables, median (25th percentile-75th percentile) for non-normally distributed continuous variables. †Repeated measures analysis of variance, ‡Friedman's analysis of variance by ranks, *Significantly different from baseline

experienced improvement in incontinence after an average of 29 months, following SIS. We observed significantly improved M-ISI scale results in our study, indicating that C-NDL improved patient-reported results, satisfaction, and life quality in women with SUI.

Regarding postoperative complications, many previous studies have demonstrated that major complications may occur during mid-urethral sling procedures, such as bleeding into the retropubic space and obturator muscle, as well as damage to the bowel and vascular system (22). However, reductions in complication rates have been observed with the use of SIS. Stanford and Paraiso (23) in their complication-related review of 20 studies and 1950 patients undergoing mid-urethral sling procedures, found a postoperative urge incontinence frequency of 15.4% (1.7-42%), and reported that preoperative anticholinergic use and advanced age were risk factors for the emergence of over-active bladder. We observed *de novo* urgency in two patients (8.3%) postoperatively, and an increase in overactive bladder symptoms in two patients. These patients received pharmacological treatment with anticholinergics, and a regression in their complaints was observed during their follow-up. A randomized controlled study reported less groin pain after SIS compared to the classical mid-urethral sling technique (24). Consistent with previous studies, groin pain was detected in only one patient (4.14%) in the early postoperative period, and the pain spontaneously regressed in the first postoperative month. Dyspareunia rates after SIS procedure are reported to be between 3-8% (25). Only one patient (4.14%) in our study group complained of dyspareunia, and during the gynecological examination, an eroded area and visible mesh were detected, explaining the dyspareunia. The incidence of urination difficulty, which is one of the important complications observed after mid-urethral sling operations, is reported to be between 0-8% in meta-analyses

Table 5. Demographics and clinical characteristics of the patients with regard to outcome

	Outcome		
Variables	**Cured (n=14)**	**Other (n=10)**	**p**
Age, years	44.79±7.60	45.40±7.43	0.846†
Body mass index, kg/m²	29.73±5.19	31.18±4.80	0.493†
Parity, n	3 (2-3)	3 (2-3)	0.756‡
History of vaginal delivery, n	11 (78.57%)	6 (60.00%)	0.393§
Giving birth to macrosomic infant, n	1 (7.14%)	1 (10.00%)	1,000§
Menopausal status			
Premenopausal, n	10 (71.43%)	7 (70.00%)	1,000§
Postmenopausal, n	4 (28.57%)	3 (30.00%)	
Sexual life			
Passive, n	3 (21.43%)	3 (30.00%)	0.665§
Active, n	11 (78.57%)	7 (70.00%)	
Gynecological operation	8 (57.14%)	6 (60.00%)	1,000§
C/S, n	8 (57.14%)	5 (50.00%)	0.651¶
TAH, n	0 (0.00%)	1 (10.00%)	
Smoking, n	5 (35.71%)	3 (30.00%)	1,000§
Diabetes mellitus, n	2 (14.29%)	0 (0.00%)	0.493§
Hypertension, n	4 (28.57%)	2 (20.00%)	1,000§
Goiter, n	2 (14.29%)	1 (10.00%)	1,000§
COPD, n	0 (0.00%)	1 (10.00%)	0.417§
Chronic constipation, n	2 (14.29%)	0 (0.00%)	0.493§
Urgency, n	7 (50.00%)	4 (40.00%)	0.697§
Duration of incontinence, years	3.5 (1-5)	4 (2-10)	0.313‡
HADS score			
Depression	7.00±4.99	9.50±3.92	0.201†
Anxiety	8.29±5.72	9.90±3.73	0.444†
Urethral funneling, n	5 (35.71%)	3 (30.00%)	1,000§
Hiatal opening, mm	56.84±6.66	55.87±7.54	0.743†
Retrovesical angle,°	137.71±16.68	144.90±31.79	0.478†
Bladder neck descent, mm	17.59±7.76	13.53±2.97	0.092†
Bladder wall thickness, mm	5.38±0.62	5.61±0.78	0.428†
Urethral rotation angle,°	71.57±12.18	72.00±10.81	0.930†
Urethral length, mm	31.37±4.94	31.72±2.84	0.843†

C/S: Caesarean section, TAH: Total abdominal hysterectomy, COPD: Chronic obstructive pulmonary disease, HADS: Hospital Anxiety and Depression Scale. Descriptive statistics were presented using mean ± standard deviation for normally distributed continuous variables, median (25th percentile-75th percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables. †Student's t-test, ‡Mann Whitney U test, §Fisher's exact test, ¶Fisher-Freeman Halton test

Table 6. Sling-related measurements of the patients with regard to outcome

	Outcome		
Variables	**Cured (n=14)**	**Other (n=10)**	**p**
Sling-bladder neck, mm	22.07±4.36	22.37±2.06	0.825†
Relative sling position, %			
1st month	70.51±9.74	70.81±7.08	0.934†
6th month	71.21±7.76	72.69±6.68	0.644†
Sling-symphysis distance, mm			
1st month	19.54±2.97	21.51±3.55	0.154†
6th month	21.20±3.36	19.87±3.37	0.170†
Sling-urethra distance, mm			
1st month	5.86±2.11	5.02±2.58	0.387†
6th month	5.31±1.36	3.72±2.16	0.071†
Sling status			
Symmetrical, n	13 (92.86%)	6 (66.67%)	0.260§
Asymmetrical, n	1 (7.14%)	3 (33.33%)	
Sling shape			
Straight line, n	11 (78.57%)	6 (66.67%)	0.762¶
Curved, n	0 (0.00%)	1 (11.11%)	
Folded "V", n	3 (21.43%)	2 (22.22%)	
Complication, n	5 (35.71%)	3 (30.00%)	1.000§

Descriptive statistics were presented using mean ± standard deviation for normally distributed continuous variables, median (25th percentile-75th percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables. †Student's t-test, §Fisher's exact test, ¶Fisher-Freeman Halton test

(26). In our study, no urination difficulties were observed in any of the patients. Our low complication rates indicate that C-NDL is a safe technique and achieves the goal of minimally invasive surgery.

A potential relationship has been shown between obesity and incontinence (particularly SUI), and it is thought that excessive body weight increases intra-abdominal pressure. However, the effect of BMI on surgical results is still controversial, and the comparability of research examining this factor is limited due to differences in follow-up, surgical approach, and cure definitions (27). Frigerio et al. (28) found that the subjective success rates were similar in different BMI categories. More than half (54.17%) of the patients in our study group were overweight and 37.50% were obese, and we did not observe a relationship between treatment success and BMI values. The absence of severely obese cases may have contributed to our results, and must be addressed in future studies.

Several clinical studies have reported a decrease in coital incontinence and an improvement in sexual activity following incontinence surgery (29). Golbasi et al. (30) demonstrated increased FSFI scores in 62 patients with SUI treated with the SIS (Ophira, Argentina) after 30 months of long-term follow-up. Contrary to the literature, no significant improvements in sexual functions were observed in our study group, as measured by baseline and sixth month FSFI scores, possibly because of the small sample size. In addition, evaluating sexual life over a specific period of time may limit understanding of how the quality of an individual's sexual experience may be affected by relational, interpersonal, situational, mood, hormonal, and habitual factors. There is a need for prolonged follow-up, including assessment of these features.

Sonographic assessment has become a crucial component of the urogynecological diagnostic examinations of patients presenting with UI in recent years. Slings can be easily visualized with perineal or introital sonography and can yield insights concerning surgical results. Ultrasonographic examination has been integrated into the postoperative evaluation of SUI patients undergoing TVT or TOT (31). Chen et al. (32) in a cumulative meta-analysis of 1,563 SUI patients, demonstrated that urethral rotation, rest and Valsalva angles, bladder neck descent, hiatus area, and bladder neck funneling were notable factors in the trans-perineal ultrasound evaluation of patients with SUI. There

are far fewer studies reporting ultrasonography findings in SIS. García-Mejido et al. (33) in their comparison of SIS patients with and without symptoms at postoperative assessment, reported significant differences in movement compliance between the sling and the urethra and in the axial tape angles at rest and at Valsalva (33). We found the urethral rotation angle value as high as 71.75±11.38° in our study group before the C-NDL procedure, and this value decreased significantly in the 1st and 6th months after surgery. However, these values were similar when compared between clinical outcome groups. This was consistent with previous studies (34). Notably, Turkoglu et al. (35) reported a mean urethral rotation angle of 86.66±11.01° in SUI patients and described that the urethral rotation angle and bladder neck descent values exhibited high specificity and sensitivity for SUI detection. In addition, we did not observe a positive relationship between the position and distance of the sling relative to the symphysis, which have been reported in TVT or TOT. For instance, mid-urethral sling success has been associated with the relative position of the sling to the urethra, and shorter sling-urethra distances have been associated with low cure or high complication rates (36). As a result, the authors suggested that the sling should be placed at least 2 mm from the urethra and between 40-70% of total urethral distance. For SIS, Kluz et al. (37) found that the relative sling position to the urethra did not differ between successful and unsuccessful cases at 36 and 50 months of follow-up. We observed that the sling-urethra distance decreased in the 6th month after surgery compared to 1 month (5.51±2.30 mm vs. 4.69±1.85 mm), but this value was not related to treatment success. Furthermore, we did not find any significant relationships between success and other ultrasonographic variables. We observed that the ultrasonography-detected outcomes of SIS were very different compared to mid-urethral slings, indicating that the classical ultrasound measurements would not be useful to assess SIS surgery outcomes; however, the low sample size and patient characteristics of our cohort should be considered before accepting this as a definite conclusion. Prospective studies with larger homogeneous sample sizes and different surgical methods are required.

The lack of correlation between USG-measured sling parameters and clinical success in our cohort may reflect several factors. First, the consistently standardized surgical technique likely minimized positional variability, reducing the ability of ultrasound to discriminate between outcomes. Second, urinary continence is determined by multiple anatomical and functional factors, including intrinsic sphincter competence and neuromuscular control, beyond sling position alone. Third, SIS such as the C-NDL have unique anchoring systems and shorter tape lengths, which may attenuate positional effects observed with retropubic or transobturator slings. Notably, prior studies of SIS have reported inconsistent or weak associations between USG parameters and clinical outcomes (33,37).

The prospective design is an inherent strength of the present study, as well as the application of all interventions by the same experienced urogynecologist. Furthermore, we used transperineal ultrasonography as well as patient-reported outcomes at follow-up examinations.

Study limitations

Several limitations should be noted. First, our cohort was limited to 24 patients-a consequence of the single-center pilot design with stringent inclusion/exclusion criteria. However, this sample size aligns with other early feasibility studies of SISs. Second, follow-up was restricted to six months to capture early efficacy and safety outcomes so long-term data are needed to confirm durability and late complications. Finally, this single-arm prospective design without a control group reflects standard practice in early-phase evaluations of novel surgical devices that prioritize feasibility and safety assessments before undertaking randomized comparisons.

Conclusion

It was demonstrated that the mini-sling procedure using the C-NDL was a reliable approach with low complications and high cure rates for SUI in women. These results indicate that short-term outcomes with SIS and C-NDL are beneficial based on quantifiable measures and patient satisfaction. However, impact on sexual functions remain unclear and there appear to be no baseline factors or ultrasonography data capable of identifying treatment success.

Ethic

Ethics Committee Approval: *All research procedures conformed to the Declaration of Helsinki and were approved by the Local Research Ethics Committee of the University of Health Sciences Türkiye, Fatih Sultan Mehmet Training and Research Hospital (approval number: 2019/19, date: 14.03.2019).*

Informed Consent: *Written and signed informed consent forms were obtained from each study participant prior to enrollment.*

Footnotes

Author Contributions: *Surgical and Medical Practices: M.Y., A.B.T., Concept: M.Y., A.B.T., Design: E.A., M.Y., Data Collection or Processing: E.A., O.S.G., Analysis or Interpretation: N.T., O.S.G., Literature Search: E.A., K.S., Writing: E.A., K.S.*

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In-depth analysis of the demographic landscape and clinical outcomes of assisted reproductive technologies in Türkiye: a comprehensive survey for the years 2020 and 2021

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Abstract

Objective: To investigate patient characteristics and outcomes of assisted reproductive technology (ART) cycles conducted in Türkiye during the coronavirus disease-2019 (COVID-19) pandemic (2020-2021).

Material and Methods: ART centers in Türkiye were invited to participate in this survey. The questionnaire focused on patient demographics and performance outcomes and was sent to center directors via anonymous Qualtrics™ links.

Results: The survey was sent to 167 centers and data were collected from 15 centers in 2020 and 24 centers in 2021. The clinical pregnancy rate from intrauterine insemination (IUI) procedures remained similar, with 15.1% in 2020 (1,245 IUI cycles) and 14.5% in 2021 (2,023 IUI cycles), while successful delivery rates were 12.5% and 11.5%, respectively. For ART treatments, the clinical pregnancy rate from fresh embryo transfers increased from 45.1% in 2020 (3,119 transfers) to 50.4% in 2021 (8832 transfers), with similar live birth rates, 34.2% vs. 34.4%. Frozen embryo transfers resulted in clinical pregnancy rates of 47.8% in 2020 (2,498 transfers) and 51.9% in 2021 (12,015 transfers), with live birth rates rising from 39.8% to 42.7%. Preimplantation genetic testing cycles resulted in clinical pregnancy rates of 64.2% in 2020 (271 transfers) and 60.8% in 2021 (2,102 transfers), with live birth rates of 53.5% and 48.2%, respectively. Regarding techniques for fertility preservation in females, 11 prepubertal and 61 postpubertal ovarian tissue cryopreservation procedures were reported, alongside 1,346 cycles performed within the same period. In males, 144 post-pubertal testicular tissue, 871 epididymal and 2,480 ejaculated sperm cryopreservations were reported. During the two years, six ovarian tissue transplantations followed by ART were performed, with 96 women using cryopreserved oocytes. In addition, 40 testicular tissue, 298 epididymal, and 238 ejaculated sperm samples were used for ART purposes.

Conclusion: This survey provides a comprehensive overview of ART practices in Türkiye for 2020 and 2021, establishing a long-term, national-level analysis while highlighting the challenges posed by the COVID-19 pandemic. The longitudinal analysis established a foundation for future annual reports and offers critical insights into emerging trends over these two years. [J Turk Ger Gynecol Assoc. 2025; 26(2): 109-15]

Keywords: Assisted reproduction techniques, medically assisted reproduction, in-vitro fertilization, registry, data collection

Introduction

The Centers for Disease Control and Prevention, the Human Fertilization and Embryology Authority, and the European Society of Human Reproduction and Embryology (ESHRE) have been publishing annual reports of assisted reproductive technology (ART) activity, which offer invaluable insights for healthcare policy making and catalyze practice changes (1-3).

2020 was a critical juncture with unique challenges posed by the coronavirus disease-2019 (COVID-19) pandemic. Clinics and healthcare systems had to adapt to a "new normal", which continuously shifted according to the trajectory of the pandemic (4,5). With limited healthcare resources, staffing modifications, and treatment protocol alterations, a comprehensive reevaluation of service delivery was imperative. Regarded as a non-emergency health service by many, fertility promoting treatments were among the first to be suspended.

Given the exceptional conditions, the 2020-2021 biennial ART data may differ significantly from prior years and provide unique insight into the pandemic period. Our recent publication of national ART trends in 2019 sets a baseline for ongoing analysis of ART activity in Türkiye. This study acts as a natural extension, offering an opportunity for direct comparison with the previous year's results (6). Such iterative data collection, a national clinical audit of ART services, is essential for observing longitudinal trends, understanding demographic shifts, and monitoring clinical outcomes.

Material and Methods

We employed the same methodology used in our previous publication on ART trends in Türkiye for 2019 (6). Briefly, questionnaire (Supplementary File 1) invitations were e-mailed to clinic directors of both public and private ART centers, employing a consolidated mailing list from relevant non-profit organizations, such as the society of reproductive health and infertility, the Turkish Society of Clinical Embryology and the Private *in vitro* fertilization (IVF) Centers Society.

Centers who did not respond were followed up including reminder calls. Data was anonymously collected both at the clinic and individual patient levels. The survey adhered to the template provided by the ESHRE (European IVF Monitoring-EIM) consortium and included an online informed consent form. The survey was administered through Qualtrics™, an internet-based commercial survey system featuring artificial intelligence-assisted adaptive inquiry methods to streamline the number of questions. Qualtrics™ incorporates security measures and protocols to prevent multiple submissions from the same participant (7). All research procedures were conducted in accordance with the Declaration of Helsinki and were approved by the Koç University Ethics Committee (approval number: 2022.386.IRB1.141, date: 07.11.2022).

Definition of terms used in the survey

Key outcome parameters for ART were delineated according to the guidelines set forth by the World Health Organization (WHO) and the International Committee for Monitoring Assisted Reproductive Technologies (ICMART). These international standards defined metrics such as clinical pregnancy, delivery timelines, and live birth rates per embryo transfer. The definitions for various categories of preterm deliveries were also incorporated, all based on the WHO/ICMART criteria (8). 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 (9).

Statistical analysis

We employed frequency measures such as count and percent in this descriptive study and did not use comparative statistical analyses.

Results

The questionnaire was shared with the directors of 167 ART centers through e-mail, featuring anonymous links supplied by Qualtrics™. Data were collected from 15 centers in 2020 and 24 centers in 2021. Data from six centers in 2020 and five centers in 2021 that provided answers to below 50% of the questionnaire's items were excluded from the final report. Much of the observed changes in treatment and clinical outcome counts between the two years result from an increased number of reporting centers, influencing counts but not rates.

Overall results per ART cycle

The outcomes, categorized by the developmental stage of the embryo at the time of embryo transfer and the number of transferred embryos in both fresh and frozen cycles, are

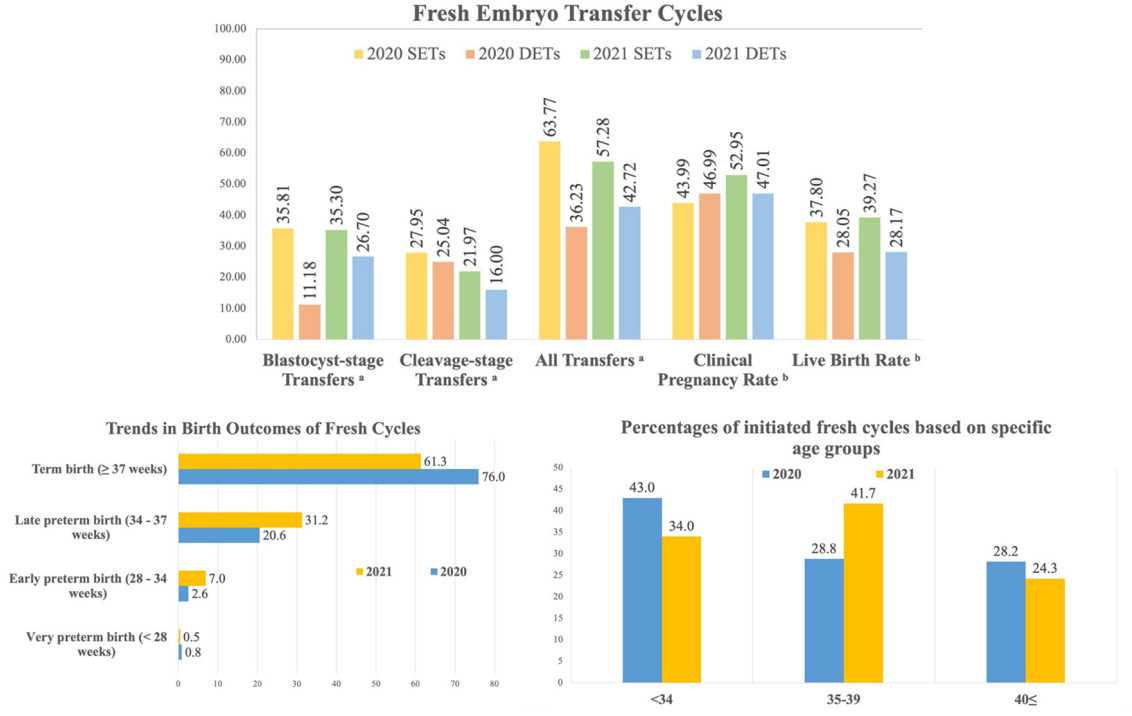

Figure 1. ART applications, trends and clinical outcomes in fresh cycles over a two-year period (all numbers are presented as rates). [a]Rates are based on all fresh embryo transfer cycles. [b]Calculated as the total number of clinical pregnancies divided by the total number of transfers for each category (e.g., clinical pregnancy rate for SETs in 2020 = number of clinical pregnancies from fresh SETs/total fresh SETs)

SET: Single embryo transfer, ART: Assisted reproductive technology

depicted in Figures 1 and 2. These figures further subdivide the data based on patient age and gestational age at delivery. In addition, the annual trend shifts in the characteristics of IVF cycles between 2019 and 2021 are illustrated in Figure 3.

Intrauterine insemination

In 2020, 1,245 intrauterine insemination (IUI) procedures were performed in 16 centers. Most (77.2%) of the female partners were below the age of 35, 20.6% between 35 and 39 years, and

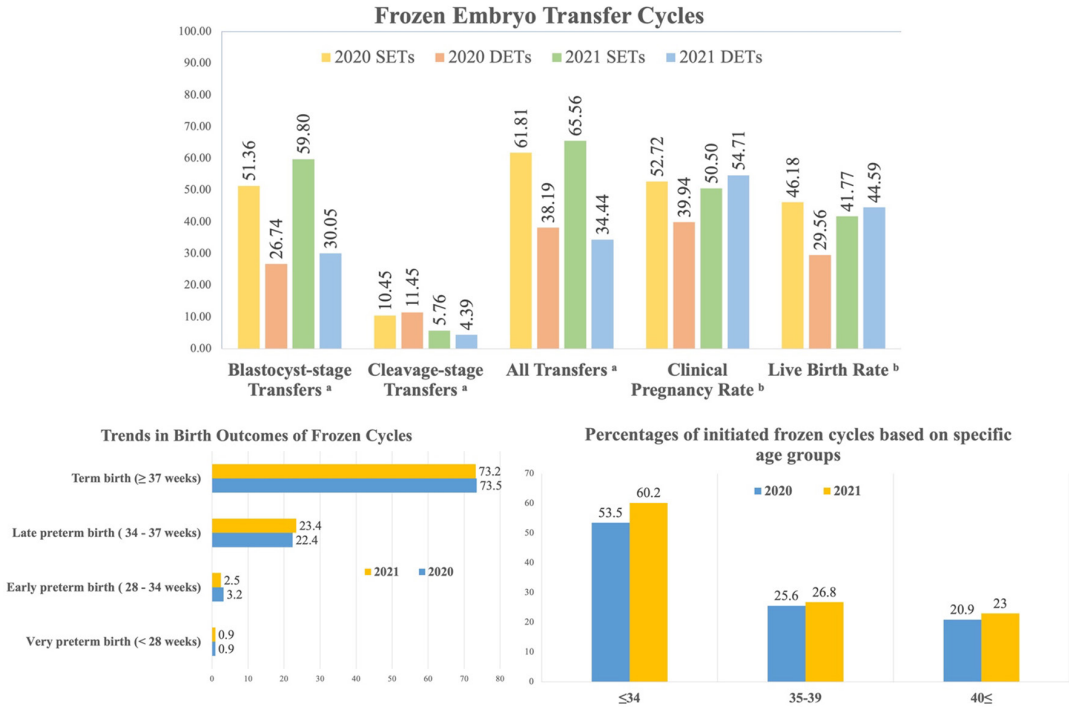

Figure 2. ART applications, trends and clinical outcomes in frozen cycles over a two-year period (all numbers are presented as rates). [a]Rates are based on all frozen embryo transfer cycles. [b]Calculated as the total number of clinical pregnancies divided by the total number of transfers for each category (e.g., clinical pregnancy rate for SETs in 2020 = number of clinical pregnancies from frozen SETs/total fresh SETs)

SET: Single embryo transfer, ART: Assisted reproductive technology

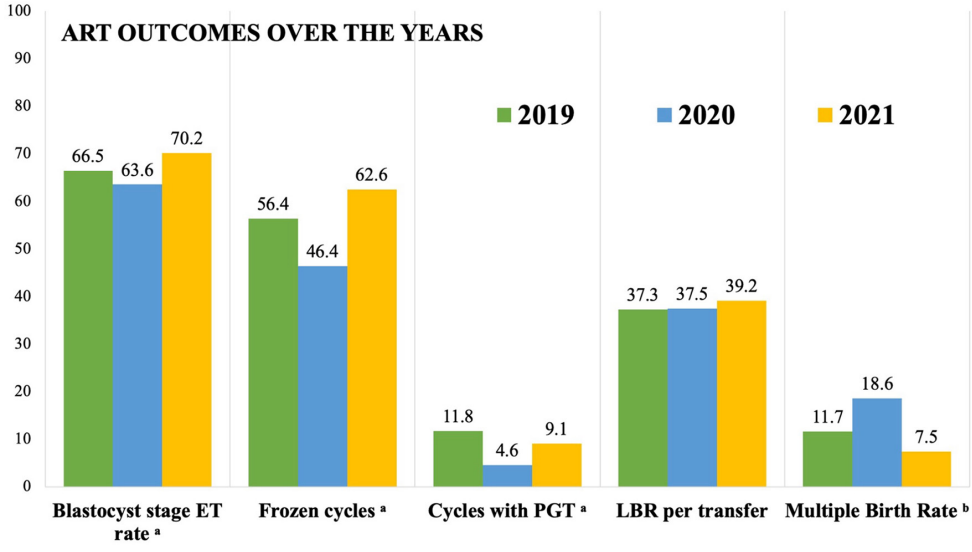

Figure 3. Trend shifts in transfer characteristics and results between 2019 and 2021. [a]Rates are based on all embryo transfer cycles. [b]Rates are based on all deliveries.

ART: Assisted reproductive technology, PGT: Preimplantation genetic test, LBR: Live birth rate, ET: Embryo transfer

only 2.2% were 40 years or older. Of the IUI cycles performed, 188 (15.1%) resulted in a clinical pregnancy, while 156 (12.5%) culminated in delivery. Among these, four were multiple births, while the outcome of seven cycles was unknown.

In 2021, 2,023 IUI cycles were performed in 24 centers, of them, 295 (14.5%) of them led to a clinical pregnancy, while 256 (12.6%) resulted in delivery. Among these births, 22 (8.6%) instances of multiple births were recorded.

Fresh cycles

In 2020, 6,502 oocyte retrieval procedures were performed across 16 centers, leading to 3,119 fresh embryo transfers using IVF or intracytoplasmic sperm injection (ICSI). Surgical sperm extraction methods-including testicular sperm extraction (TESE), micro-TESE, and fine-needle aspiration-were used in 199 instances. Among the fresh embryo transfers, a single embryo was transferred in 1,989 cases (63.7%). There were 1,406 clinical pregnancies (45.1%), with 272 pregnancy losses (19.3%) and 1,069 live births (34.2%) occurred from all fresh transfers. Among deliveries 183 (17.1%) resulted in multiple births. Pregnancy outcomes were missing for 65 cycles.

In 2021, the number of oocyte retrieval procedures increased to 22,368 across 24 centers, leading to 8,832 fresh embryo transfers after IVF or ICSI. Surgical sperm extraction was performed in 1,476 instances. Single embryo transfers were carried out in 5,059 cases (57.2%), showing a slight decrease in the single embryo transfer rate from the previous year. There were 4,453 clinical pregnancies (50.4%), with 400 pregnancy losses (9.0%) and 3,050 live births (34.5%) derived from all fresh transfers. Among deliveries, 314 (10.2%) resulted in multiple pregnancies. While the multiple pregnancy rate was notably decreased compared with the previous year, pregnancy outcomes were missing for a higher proportion of transfers (1003/8832-11.3% in 2021 vs. 65/3119-2% in 2020) cycles.

Frozen cycles

In 2020, 2,573 thawing procedures were carried out, leading to 2,498 embryo transfers. Single-embryo transfers accounted for 1,544 cases (61.8%), 1,195 clinical pregnancies (47.8%), 96 pregnancy losses and 995 live births (39.8%) were derived from frozen embryo transfers. 21.7% of all births resulted in multiple deliveries, and there were 104 cycles with missing pregnancy outcomes.

In 2021, a total of 12,560 thawing procedures were performed, resulting in 12,015 embryo transfers. Out of these transfers, 7,877 (65.5%) were single-embryo transfers. From the frozen cycles, there were 6,242 clinical pregnancies (51.9%), 890 pregnancy losses and 5,135 live births (42.7%). Additionally, 535 (10.3%) of the live births were multiple deliveries. The pregnancy outcomes for 217 cycles were not available.

Cycles with PGT

The survey did not seek information concerning the preimplantation genetic test (PGT) results, i.e., whether the transferred embryo had been diagnosed as euploid or mosaic. In 2020, 174 clinical pregnancies (64.2%) were achieved from 271 PGT transfers, with 145 (53.5%) resulting in live births. In 2021, 1,280 clinical pregnancies (60.8%) were reported from 2,102 PGT transfers, leading to 1,014 live births (48.2%).

Complications during ART and fetal reduction procedures

Over the two years, 119 women were hospitalized for OHSS stage 3 or higher. Of these, 95 women were admitted due to hemorrhage, and 12 were admitted for infections. None of these cases led to mortality, and no selective fetal reduction procedures were performed.

Data from international patients

International patient cycles increased from 1,250 in 2020 to 4,613 in 2021, predominantly from Azerbaijan, Bulgaria and Syria. These couples' primary countries of residence are as follows: Azerbaijan 19.6%, Bulgaria 11.2%, Syria 9.1%, Germany 4.4%, Libya 2.5%, and Iraq 2%-the remaining 3,302 couples, came from other countries. The survey also explored the reasons for seeking treatment abroad, revealing that 1,955 couples (58.2%) chose to undergo treatment in Türkiye primarily due to the lower cost of procedures. Other influencing factors included distance, waiting lists (141 couples-4.1%), treatment quality, and previous treatment failures (1,258 couples-37.5%).

Fertility preservation

The data collection format does not provide information about the storage date of gametes or gonadal tissue that were used in the study period.

In 2020, seven prepubertal and 29 postpubertal ovarian tissue cryopreservation procedures were performed, along with 294 oocyte cryopreservation cycles. Moreover, 94 postpubertal testicular tissue cryopreservation procedures, eight epididymal, and 299 ejaculated sperm cryopreservation procedures were documented. For females, two ovarian tissue auto-transplantation procedures (followed by ART) were performed, and 26 women used their cryopreserved oocytes. For males, 11 testicular tissue, 23 epididymal, and 42 ejaculated sperm samples were used.

In 2021, reports included four prepubertal and 32 postpubertal ovarian tissue cryopreservation procedures, along with 1,054 oocyte cryopreservation cycles. In males, 50 postpubertal testicular tissue cryopreservation procedures, 863 epididymal, and 2181 ejaculated sperm cryopreservation procedures were documented. For females, four ovarian tissue auto-transplantation (followed by ART) were performed, and 70

women used their cryopreserved oocytes. Furthermore, 29 testicular tissue, 275 epididymal, and 196 ejaculated sperm samples were used.

Discussion

Our survey collected data from 15 and 24 ART centers in Türkiye for 2020 and 2021, respectively. The primary objective of the survey was to offer a demographic landscape and a detailed record of ART treatments rather than to rank centers or treatment methods. According to the Turkish Statistical Institute data from 2020-2021, the proportion of women of reproductive age (15-45 years) to the total population was 26.2%, and 1,113,658 births were recorded. Over a two-year period, the total number of reported clinical pregnancies and live births increased, while the live birth rates remained stable. The visible reduction in multiple pregnancy rates in both fresh and frozen cycles is a positive development. It reflects the successful implementation of the single embryo transfer policy and improved embryo selection techniques. However, the increase in number of cycles with missing pregnancy outcomes is a concern, as this may affect the accuracy of success rates and outcome assessments. This highlights the need for improved data collection and patient follow-up protocols in the future to ensure comprehensive reporting.

The society for assisted reproductive technology (SART) released its 2020 reports for infertility treatments in the United States in 2022 (10). Based on these, excluding donation cycles, live birth rates following egg retrieval were 54.5% for women under 35, 39.8% for ages 35-37, 26.1% for ages 38-40, 13.3% for ages 41-42, and 4.0% for those above 42 years old, and overall singleton delivery rate was 94.74%. In comparison, our results show a live birth rate of 48.5% for women under 35, 35.3% for those aged 35-39, and 9.8% for those over 40 years old, and the overall singleton delivery rate was 81.0%, all parameters lower than the SART annual data. This comparison provides a global perspective on the outcomes of ART treatments in Türkiye.

Study limitations

The COVID-19 pandemic had a profound impact on the case volume and practice patterns in in the United Kingdom (11). Private clinics were quicker to reopen, compared with National Health Service clinics (83 vs. 34% respectively). The annual number of fresh cycles decreased by 28%, and storage of embryos increased by 6%, the later being the only ART-related activity showing an increase from 2019 to 2020. Although the resemblances might occur in Türkiye, we cannot demonstrate reopening trends or overall shifts in the total number of ART cycles due to the relatively small numbers of ART clinics contributing to the data collection. This data reflects the real-time impact of the pandemic on ART treatments. The 2021 report features a 14.3% participation rate from ART centers and maintains methodological consistency by employing a robust questionnaire based on ESHRE EIM consortium guidelines. Accumulating data allows for a temporal comparison and also adds fertility preservation as a new and important outcome compared to last year's survey in ART practices. This addresses a limitation in the 2019 survey and enhances the depth of the findings.

Conclusion

This survey provided a comprehensive vision of ART practice in Türkiye, serving as a stepping-stone for long-term, national-level scrutiny in this field. It is hoped that eventually it will offer a comprehensive perspective as the survey evolves and the annual reports continue. Furthermore, capturing the data for the pandemic years allowed a comparison with data from 2019, a pre-COVID-19 baseline year. These ongoing clinical audit efforts intend to lay the foundation for a detailed, more insightful, annual reporting system-one we hope will engage a broader array of participants to provide quality healthcare to patients.

Ethic

Ethics Committee Approval: *All research procedures were conducted in accordance with the Declaration of Helsinki and were approved by the Koç University Ethics Committee (approval number: 2022.386.IRB1.141, date: 07.11.2022).*

Informed Consent: *The survey adhered to the template provided by the ESHRE (European IVF Monitoring-EIM) consortium and included an online informed consent form.*

Footnotes

Author Contributions: *Surgical and Medical Practices: A.Y., B.M.S., B.G., B.S., D.A., D.S., D.K., E.A., E.E., G.H.C., G.I., G.A.S., I.M., K.S., M.S., O.K., S.E., S.Y.E., T.V., U.G., U.B., U.E., B.B., A.B., Concept: B.C., B.B., A.B., Design: B.C., B.B., A.B., Data Collection or Processing: B.C., B.B., A.B., Analysis or Interpretation: B.C., A.B., Literature Search: B.C., B.B., A.B., Writing: B.C., A.B.*

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The effect of COVID-19 (SARS-CoV-2) vaccines on vulvar condylomata

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Abstract

Objective: Current evidence concerning the possible clinical effects of coronavirus disease-2019 (COVID-19) vaccines on vulvar lesions is limited. The aim was to describe the effect of vaccines against COVID-19 on the progression of vulvar condylomas.

Material and Methods: The data of patients diagnosed with condylomata acuminate and treated with trichloroacetic acid (TCA) between January 2021 and January 2023 in the gynecological oncology surgery clinic were evaluated. The patients were divided into groups based on their vaccination status; vaccinated or unvaccinated. The number/area of condylomas and symptom degrees of the patients before and after TCA treatment were compared.

Results: A total of 202 patients, 102 vaccinated and 100 unvaccinated, were included. There was no significant difference between the groups in terms of age, parity, smoking, oral contraceptive use, amount of condyloma and symptom degree (all $p>0.05$). There was no significant difference in the amount of condyloma between the groups after six months [$p=0.589$, 95% confidence interval (CI)=0.238-1.566]. Moreover, there was no difference in the degree of symptoms after six months between the groups ($p=0.467$, 95% CI=1.113-1.799).

Conclusion: The systemic effects caused by COVID-19 vaccines are still not fully understood. Considering that this vaccine, like many vaccines, elicits a strong immunogenic reaction, the possible clinical impact of this non-specific systemic inflammatory response on vulvar condyloma is a matter of curiosity. This study showed there was no difference in the amount of condyloma and the degree of symptoms six months after TCA treatment in the unvaccinated and vaccinated group. The low number of patients is the biggest limitation of this study. Larger studies may provide more robust information. [J Turk Ger Gynecol Assoc. 2025; 26(2): 116-20]

Keywords: COVID-19 vaccines, vulvar condyloma, skin diseases

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Introduction

Coronavirus disease-2019 (COVID-19) is an infectious respiratory disease caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), which emerged in late 2019 and became a global pandemic. Lymphocytopenia observed during infection often involved CD4+ and some CD8+ T-cells, disrupting both innate and adaptive immune responses. This disruption may delay viral clearance and lead to an exaggerated neutrophilic and macrophagic response (1). In Türkiye, three vaccines were approved for use against COVID-19. The Pfizer/BioNTech vaccine, an mRNA-based vaccine, stimulated an immune response by injecting a genetic code encapsulated in lipid nanoparticles that encodes the viral spike protein. The CoronaVac (Sinovac) vaccine was an inactivated vaccine developed by culturing and then inactivating the live SARS-CoV-2 virus under laboratory conditions. The domestically developed, inactivated vaccine, Turkovac, was approved for routine use following a scientific review by the Turkish Ministry of Health.

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Genital warts and condyloma acuminatum (CA) are superficial benign lesions of the skin. Most commonly associated with human papilloma virus (HPV) types 6 and 11. The prevalence of CA peaks during the early years of sexual activity. Identified risk factors include smoking, hormonal contraceptive use, multiple sexual partners, and early onset of sexual activity. These lesions are typically multicentric and multifocal, involving the perianal, vaginal, and cervical regions, but may also affect the oral and laryngeal mucosa. Most patients are asymptomatic, presenting primarily with painless swellings, and less frequently with itching, discharge, or bleeding. Common treatment options include provider-administered therapies (cryotherapy, electrocautery, laser, and/or surgical excision) and patient-applied treatments (chemotherapeutic agents or immunomodulatory therapies) (2).

The immunological response triggered by COVID-19 vaccines and the resulting clinical implications have yet to be fully elucidated. Despite the growing body of knowledge and clinical experience acquired during the pandemic, the immunological impact of anti-SARS-CoV-2 vaccines remains incompletely understood, highlighting the need for further research. The aim of the present study was to investigate the potential effect of SARS-CoV-2 vaccination of vulvar condylomas.

Material and Methods

The data of women diagnosed with CA and treated with trichloroacetic acid (TCA) at the Gynecologic Oncology Surgery Clinic between January 2021 and January 2023 were evaluated. The data were obtained retrospectively by talking to the patient face to face or from the electronic database system. All participants gave their informed written consent to take part in the study. This study was approved by the Non-Interventional Clinical Research Ethics Committee of Konya City Hospital (approval number: 2025/30, date: 10.03.2025).

Women aged 16-65 years who were diagnosed with vulvar condylomas by clinical examination or biopsy, treated exclusively with TCA, had documented treatment and follow-up processes, and had no underlying medical conditions or medication use that could impair immune response were included in the study. Patients who received any other medical or surgical treatment for condylomas besides TCA, or those with comorbidities or medications that could suppress immune response, were excluded.

Participating patients were divided into COVID-19 vaccinated and unvaccinated groups. In both the vaccinated and unvaccinated groups, patient age, parity, smoking status, oral contraceptive use, number of condylomas, and severity of symptoms were analyzed.

The amount of condyloma was assessed by evaluating both the number, and the total surface area, of the lesions. Patients with 1-5 lesions or a total surface area of less than 1 cm^2 were categorized as having a limited amount of condylomas; those with 6-10 lesions or a surface area between 1-3 cm^2 were considered to have a moderate amount; and those with more than 10 lesions or a surface area greater than 3 cm^2 were classified as having widespread condylomas. Symptoms were also classified into mild, moderate, and severe based on patient complaints.

Vulvar lesion progression after COVID-19 vaccination was assessed as follows: (a) complete response: complete resolution of lesions and no new lesions; (b) partial response (PR): at least 30% reduction in lesion size, number, or symptoms; (c) stable disease: PR or no evidence of progressive disease (PD) in symptoms and lesions during the study; (d) PD: at least 20% increase in symptoms and lesion size or number, no new lesions.

Statistical analysis

SPSS, version 22, was used to evaluate the data (IBM Corporation, Armonk, NY, USA). Analysis results are shown as mean, standard deviation, n (number) and % (percentage). Frequency distributions were analyzed according to groups with chi-square test and Fisher's exact test. A value of $p<0.05$ was considered statistically significant.

Results

A total of 266 women were assessed for eligibility. Forty-six individuals were excluded either for not meeting the inclusion criteria or for declining to participate. The remaining 220 (82.7%) women with high-risk HPV infection were enrolled and divided equally into vaccinated (n=110) and unvaccinated (n=110) groups. During follow-up, eight women in the vaccinated group and 10 in the unvaccinated group were excluded from the final analysis due to lost to follow-up or discontinuation of treatment. The flow diagram of patient selection is presented in Figure 1.

There were no significant differences between the vaccinated and unvaccinated groups in terms of age, parity, smoking status, oral contraceptive use, condyloma amount, or symptom severity. Table 1 shows the clinicopathological and demographic characteristics of the patients.

Six months after treatment, the rates of clinical response in terms of condyloma quantity in the unvaccinated and vaccinated groups were statistically similar. A summary of post-treatment amount of condyloma and symptom severity at six months after TCA treatment is presented in Table 2.

Discussion

According to the GLOBOCAN 2018 report, HPV ranks as the second most common infectious agent associated with cancer

Table 1. Demographic and clinico-pathological characteristics of patients vaccinated/not vaccinated against COVID-19				
		COVID-19 vaccine		
		No (n=100)	**Yes (n=102)**	
Features		**Mean ± SD**	**Mean ± SD**	**p**
Age (years)		32.88±11.99	34.30±11.98	0.679
Parity		1.32±1.20	1.21±1.14	0.524
		n (%)	n (%)	
Smoking		44 (44)	47 (46.1)	0.738
Oral contraceptive		29 (28.4)	34 (33.3)	0.315
Amount of condyloma	Limited	39 (39)	32 (31.3)	0.228
	Moderate	53 (53)	60 (58.8)	
	Widespread	10 (10)	6 (5.8)	
Symptom degree	None	9 (9)	12 (11.7)	0.398
	Mild	30 (30)	23 (22.5)	
	Moderate	44 (44)	54 (52.9)	
	Severe	17 (17)	13 (12.7)	
p: Chi-square test, SD: Standard deviation, COVID-19: Coronavirus disease-2019				

Table 2. The number of condylomas and degree of symptoms in the vaccinated and unvaccinated patients after six months

Features		**COVID-19 vaccine**			
		No (n, %)	**Yes (n, %)**	**95% CI**	**p**
Amount of condyloma	CR	64 (62.7)	72 (70.5)	0.238-1.566	0.589
	PR	28 (27.4)	20 (19.6)		
	SD	6 (5.9)	7 (6.8)		
	PD	2 (2)	3 (2.9)		
Symptom degree	CR	78 (76.5)	70 (68.6)	1.113-1.799	0.467
	PR	16 (15.7)	22 (21.5)		
	SD	4 (3.9)	6 (5.9)		
	PD	2 (2)	4 (3.9)		
Chi-square test, p: Significance value, p: 0.05, CI: Confidence interval, CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease					

development worldwide, in both sexes. Furthermore, HPV is the leading infectious cause of cancer in women. Inflammatory processes play an active role in the persistence of HPV infections.

Patients infected with COVID-19 have shown elevated leukocyte counts and abnormally increased levels of cytokines and chemokines (3). The systemic consequences of the enhanced inflammatory response remain incompletely understood.

The World Health Organization reported that anti-vaccination sentiment existed, even during the peak of the COVID-19 pandemic. Although vaccine manufacturers reported low rates of adverse effects, the systemic effects of COVID-19 vaccines have yet to be fully elucidated. While COVID-19 infection is primarily known to cause interstitial pneumonia and potentially severe respiratory failure, it has also been associated with various cutaneous manifestations. The long term effects of infection with the virus, regardless of vaccination status, are also unknown and yet to be elucidated.

Dermatological adverse reactions and various cutaneous diseases have been reported after COVID-19 vaccination. Type I and type IV hypersensitivity reactions were among the main cutaneous side effects (4). In a study by Sartor et al. (2), cases of vulvar aphthous ulcers characterized by vulvar pain and dysuria following Pfizer-BioNTech vaccination were reported (5). Since the COVID-19 vaccine can trigger a strong immunogenic reaction, the possible impact of this non-specific systemic inflammatory response on the clinical course of vulvar condyloma is of interest.

To the best of our knowledge, this is the first published study investigating the potential impact of COVID-19 vaccination

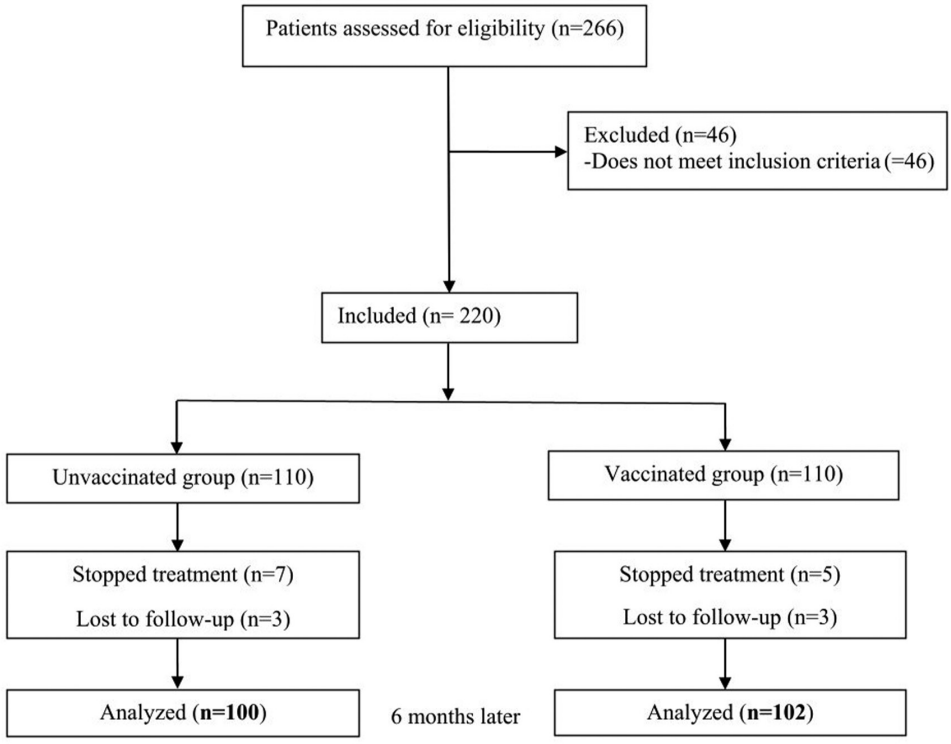

Figure 1. Process flow chart for patient

on the clinical course of vulvar condyloma. Reassuringly, Our findings revealed no significant difference between the vaccinated and unvaccinated groups in terms of condyloma quantity and symptom severity at six-month follow-up after treatment with TCA [95% confidence interval (CI): 0.238-1.566, p=0.589 and 95% (CI): 1.113-1.799, p=0.467, respectively].

Study limitations

The small number of patients is the biggest limitation of the study. Its retrospective design may also be considered a limitation.

Conclusion

There was no significant effect of COVID-19 vaccination on the progression of vulvar condylomas. The effects of COVID-19 vaccines on vulvar lesions have not been elucidated in the current literature and this appears to be the only study in this field. Therefore, further comprehensive, long-term studies are warranted.

Ethic

Ethics Committee Approval: *This study was approved by the Non-Interventional Clinical Research Ethics Committee of Konya City Hospital (approval number: 2025/30, date: 10.03.2025).*

Informed Consent: *All participants gave their informed written consent to take part in the study.*

Footnotes

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

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Predictive efficacy of rectus abdominis muscle and psoas major muscle thickness for postoperative morbidity in patients with endometrial cancer

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Abstract

Objective: The association between skeletal muscle mass and postoperative morbidity in cancer patients has been demonstrated, but the results are not conclusive. The study aims to determine the predictive efficacy of rectus abdominis muscle (RAM) and psoas major muscle (PMM) thickness and other factors such as age, American Society of Anesthesiologists (ASA) score, operation duration, obesity, preoperative inflammatory markers, and pathological findings for postoperative morbidity.

Material and Methods: One hundred forty-one patients who underwent total abdominal hysterectomy + bilateral salpingo-oophorectomy + retroperitoneal lymphadenectomy + omentectomy for endometrial cancer were assessed retrospectively. Standard procedures (antibiotic prophylaxis and thromboembolism prophylaxis) were applied pre- and postoperatively, and the thicknesses of the RAM and PMM were measured by computed tomography. Postoperative morbidity was defined in the 3-month postoperative period as patients treated with a diagnosis of postoperative infection, those who developed pulmonary complications, thromboembolic complications, lymphatic drainage disorders, intracranial hemorrhage, and mortality.

Results: The mean thickness of the right-left RAM in the morbidity group was 7.4±2.1 mm, and 8.2±2.1 mm in the group without morbidity (p=0.038). On the other hand, the thickness of the right-left PMM was similar in both groups. When the predictive cut-off value for RAM thickness was 7.52 mm, the sensitivity, specificity, and negative and positive predictive values were 54.2%, 65.6%, 73.5%, and 44.8%, respectively. Advanced age, high ASA score, and extended operation duration were associated with an increased risk of morbidity in univariate analysis. However, multivariate analysis revealed that only age and operation duration were independent risk factors for postoperative morbidity [respectively, odds ratio (OR): 1.06, 95% confidence interval (CI): 1.01-1.12, p=0.033 and OR: 1.003, 95% CI: 1.0003-1.007, p=0.039].

Conclusion: Age and operation duration were identified as independent risk factors for predicting postoperative morbidity. However, it has been shown that a more comprehensive evaluation, including RAM thickness and ASA score alongside these two factors, could provide more definitive results. [J Turk Ger Gynecol Assoc. 2025; 26(2): 121-9]

Keywords: Endometrial cancer, postoperative morbidity, sarcopenia, rectus abdominis muscle, psoas major muscle

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Introduction

Endometrial cancer is the most common gynecological cancer in developed countries and the second most frequent after cervical cancer in developing nations. Approximately 287,100 new cases are diagnosed annually worldwide (1). About 70% of these patients are identified at an early stage, with a 5-year survival rate of 80%, while those at stages IVA and IVB have 5-year survival rates of 17% and 15%, respectively (2).

The primary treatment for endometrial cancer is surgical, and it includes hysterectomy, bilateral salpingo-oophorectomy and lymphadenectomy in patients deemed at risk for extrauterine disease (3). These surgeries can be performed using laparoscopic, robotic, or open abdominal techniques. Surgical complications may include surgical site infections, thromboembolism (pulmonary emboli, deep vein thrombosis), and pulmonary complications (atelectasis, pulmonary disease). The rate of postoperative morbidity in patients undergoing primary surgery is reported to be between approximately 14% and 21% (4).

The likelihood of developing postoperative surgical site infections and other complications vary based on age, incision type, surgical procedure, operation duration, intraoperative hemorrhage volume, preoperative antibiotic prophylaxis, and the patient's comorbidities (5). Moreover, conditions characterized by low skeletal muscle mass, such as sarcopenia and myosteatosis, marked by increased fat and fluid infiltration into muscle, reflect reduced energy reserves and inadequate nutrition and are associated with chronic systemic inflammation (5-7). Sarcopenia has been shown to be associated with prolonged mechanical ventilation, longer stays in hospitals and intensive care units, postoperative complications, and increased mortality (8,9). Consequently, inadequate muscle mass has been linked to increased postoperative morbidity and mortality (10-12).

The European Consensus (European Working Group on Sarcopenia in Older People) defines computed tomography (CT) and magnetic resonance imaging as the gold standards for estimating muscle mass (13). According to the same consensus, measuring skeletal muscle area in images is a valid criterion for estimating muscle mass (13). Additionally, measurements of the thickness of the rectus abdominis muscle (RAM) have been shown to identify sarcopenia (14), and similarly, the thickness of the psoas major muscle (PMM) is a marker of skeletal muscle mass (15).

Few studies have investigated the impact of the RAM on morbidity in cancer patients. Zhuang et al. (16) demonstrated that RAM thickness was significantly different between groups with and without postoperative morbidity in patients undergoing radical resection for colorectal cancer, thus identifying it as a significant predictive factor for postoperative complications. Liu et al. (17) have also identified preoperative RAM thickness as being associated with postoperative morbidity in patients undergoing surgery for colon cancer. However, Shachar et al. (18) found that patients with a thicker RAM had a higher risk of surgical site infections in adult solid tumors. They suggested that this might be due to increased blood flow in the muscle tissue leading to higher bacterial colonization and infection risk (18). Thus, the effectiveness of RAM thickness as a predictor of postoperative morbidity remains unclear.

This study primarily aims to define the impact of CT-measured thickness of the RAM and PMM on postoperative morbidity in patients undergoing surgery for endometrial cancer. Secondarily, it explores the role of other factors [American Society of Anesthesiologists (ASA) score, age, duration of operation, obesity, preoperative inflammatory markers, and pathological findings] in determining postoperative morbidity.

Material and Methods

In this study, we retrospectively analyzed patients who underwent elective laparotomy for endometrial cancer between September 2019 and April 2023, after ethical approval was obtained for the study. Ethical approval was granted by the Ethics Committee of Ankara Bilkent City Hospital (approval number: E2-23-4349, date: 19.07.2023). Patient data were retrieved from the hospital's electronic data-based system, pathology reports, and patient files. Staging was performed according to the International Federation of Gynecology and Obstetrics (FIGO) 2009 system.

The study group comprised 141 patients who met the predefined inclusion criteria. Included ones were those who underwent surgical procedures involving total abdominal hysterectomy + bilateral salpingo-oophorectomy + retroperitoneal lymphadenectomy + omentectomy through a xiphopubic median incision and had undergone abdominopelvic imaging with CT in the month preceding surgery. Patients who underwent surgery through any incision other than a xiphopubic median incision, those treated with minimally invasive surgical techniques (laparoscopic or robotic), those without a CT scan of the abdominopelvic in the month prior to surgery, those who have not undergone total abdominal hysterectomy + bilateral salpingo-oophorectomy + retroperitoneal lymphadenectomy + omentectomy in the surgical procedure, those who underwent additional cytoreductive surgical procedures, those whose final pathology included a sarcoma component, and those with diagnosed synchronous tumors were excluded from the study.

Preoperative thromboembolism prophylaxis for the patients included administration of low molecular weight heparin subcutaneously according to the Caprini scoring system

(19), and 2 grams of cefazolin intravascularly 30 minutes before skin incision. Patients allergic to cefazolin were given a combination of gentamicin and clindamycin. Postoperative morbidity was defined as occurring within 3 months after surgery and included postoperative infections (surgical site infections; deep surgical site infections, incision line infections, cellulitis, subcutaneous abscess, psoas major abscess, non-surgical site infections; pulmonary or other system infections), atelectasis, thromboembolic complications (deep vein thrombosis, pulmonary thromboembolism, cerebrovascular emboli), lymphatic drainage disorders (chylous ascites and lymphangitis), intracranial hemorrhage, and mortality.

Muscle measurements

Preoperative CT images were used to measure each patient's right and left RAM and PMM. These measurements were taken at the broadest cross-section of the muscles, identified at the level of the L_{4-5} intervertebral disk in the axial section. The arithmetic mean of the measurements for each muscle was calculated and recorded in the database.

Statistical analysis

Statistical analyses were performed using SPSS v26, with a p-value of <0.05 considered statistically significant. The distribution of continuous variables was examined using histograms and the Shapiro-Wilk test. Variables that conformed to a normal distribution were presented with mean and standard deviation, whereas those that did not conform were described using median and range. Categorical variables were expressed as numbers and %. Differences between two independent groups were analyzed using the independent t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. The chi-square test was employed to compare categorical variables. Logistic regression was conducted to predict morbidity, and the effects of independent variables were presented as odds ratios with 95% confidence intervals (CIs). The diagnostic performance of variables was assessed using the receiver operating characteristic (ROC) curve and the area under curve (AUC) values. Optimal sensitivity and specificity were determined using the Youden Index method.

Results

The mean age of the patients was 63.6±9.1 years (range: 34-84 years). The mean tumor size was 5.6±3.1 cm (range: 0.3-18 cm). It was found that 93 patients (66%) had endometrioid-type endometrial cancer according to the final pathology. Fifty-two (36.9%) patients were staged as stage I, while 14 (9.9%) were at stage IV. The median number of total lymph nodes removed was 45 (range: 8-126). Pelvic and/or paraaortic lymph node metastasis were identified in 40 (28.4%) patients, cervical stromal and/or glandular invasion in 29 (20.6%), lymphovascular space invasion in 49 (34.8%), and adnexal spread in 22 (15.6%). Positive peritoneal cytology was recorded in 13 (9.2%) patients (Table 1).

The mean body mass index (BMI) was 32.2±6.6 kg/m^2 (range: 21-62 kg/m^2). The mean operation time was 259.6±108.6 minutes (range: 90-680 minutes), the mean perioperative red blood cell transfusion was 0.2±0.7 units (range: 0-4 units), and the mean perioperative fresh frozen plasma transfusion was 0.1±0.4 units (range: 0-3 units). The mean ASA score was 2.2±0.6 (range: 1-4). The mean thickness of the right-left RAM was measured at 7.9±2.2 mm (range: 3.3-13.5 mm), and the mean thickness of the right-left PMM was 32.1±4.8 mm (range: 20.8-42.8 mm) (Table 2).

One hundred and eight (76.6%) patients had at least one comorbidity. The three most common comorbidities were hypertension in 89 (63.1%) patients, diabetes mellitus in 52 (36.9%), and asthma in 10 (7.1%) (Table 3).

Morbidity and mortality data

Morbidity occurred in 48 (34%) patients and mortality in 3 (2.1%). Two patients developed more than one morbidity. The most common causes of morbidity were non-surgical site infections (n=17, 35.4%), surgical site infections (n=11, 22.9%), and atelectasis (n=5, 10.4%) (Table 4). All mortality cases were due to pulmonary thromboembolism. These 3 patients were in the geriatric age group with an ASA score of 3. The pathology results for 2 of the deceased were reported as endometrioid adenocarcinoma and for 1 as serous adenocarcinoma. Two deaths occurred within 7 days postoperatively, while one occurred on postoperative day 42.

Laboratory findings were similar between groups with and without morbidity development. However, the morbidity group was older, had longer operation times, higher ASA scores, and a lower mean RAM thickness than the non-morbidity group (Table 5). The mean age in the morbidity group was 66.6±7.8 years versus 62.1±9.3 years in the non-morbidity group (p=0.005). The operation time was longer in the morbidity group, with a mean of 287.9±114.7 minutes compared to 245.1±103 minutes in the non-morbidity group (p=0.026). The ASA score was higher in the morbidity group, with a mean of 2.3±0.6 compared to 2.1±0.6 in the non-morbidity group (p=0.038). The mean thickness of the right-left RAM was significantly lower in the morbidity group compared to the non-morbidity group (7.4±2.1 vs. 8.2±2.1 mm; p=0.039). However, PMM thickness did not predict morbidity; the mean thickness in the morbidity group was 31.8±4.8 mm, compared to 32.3±4.9 mm in the non-morbidity group (p=0.614). No significant differences were

Table 1. Age and pathological characteristics of endometrial cancer

Parameters	Mean ± SD	Median	Range
Age, years	63.6±9.1	64	34-84
Tumor size, cm	5.6±3.1	5	0.3-18
Number of removed lymph nodes	47.7±19.1	45	8-126
		n	%
Tumor types	Endometrioid/serous type	93/37	66/26.2
	Clear cell/mixed type	4/5	2.8/3.8
	Other types	2	1.4
Stage-FIGO 2009	$I_A/I_B/II$	52/31/5	36.9/22/3.5
	III_A/III_B	6/3	4.3/2.1
	III_{C1}/III_{C2}	6/24	4.3/17
	IV_A/IV_B	3/11	2.1/7.8
Depth of myometrial invasion	No invasion	8	5.7
	<1/2	58	41.1
	≥1/2[1]	69	48.9
	Uterine serosa	6	4.3
Cervical invasion	No invasion	112	79.4
	Glandular	1	0.7
	Stromal/glandular	28	19.9
Lymphovascular space invasion	Negative/positive	92/49	65.2/34.8
Peritoneal cytology	Negative/positive	128/13	90.8/9.2
Adnexal metastasis	Negative/positive	119/22	84.4/15.6
Lymph node metastasis	Negative	101	71.6
	Pelvic only	6	4.3
	Paraaortic only	4	2.8
	Pelvic and paraaortic	30	21.3

[1]: Excluding uterine serosa. FIGO: International Federation of Gynecology and Obstetrics, SD: Standard deviation

found between the two groups regarding perioperative red blood cell and fresh frozen plasma use (p=0.341, p=0.440, respectively) (Table 5). Hypertension, diabetes mellitus, tumor type, and FIGO 2009 stage showed no association with morbidity development (Table 6).

Receiver operating characteristic analysis

In the ROC analysis (Figure 1), the AUC for the mean thickness values of the right-left RAM was found to be significant (p<0.05). The optimal cut-off value for RAM thickness was calculated to be 7.52 mm. The 95% CI sensitivity was 54.2%, and specificity was 65.6%. The positive predictive value was 44.8%, and the negative predictive value was 73.5%. When employing a threshold of 7.52 mm, the risk of morbidity development increased from 26.5% to 44.8% (p=0.024). These findings indicate that the mean thickness of the right-left RAM has a moderate performance in predicting morbidity.

Regression analysis

When a logistic regression model was constructed to predict morbidity using age, average values of the right-left RAM, ASA, and operation time were used as variables, and age and operation time were independent predictors of morbidity. An increase of one unit in age increased the risk of morbidity by 1.06 (95% CI=1.01-1.12; p=0.033), and an increase of one unit in operation time increased the risk by 1.003 (95% CI=1.0003-1.007; p=0.039) (Table 7).

Discussion

The present study, aimed at evaluating the predictive capacity of CT-measured RAM and PMM thicknesses for postoperative morbidity in patients undergoing surgery for endometrial cancer, appears to be the first of its kind according to the current literature. Our findings indicate that the non-morbid group had a higher mean thickness of the right-left RAM than those who developed morbidity (8.2 mm vs. 7.4 mm;

Table 2. Demographic, laboratory, and muscle thickness characteristics of patients

Parameters	Mean ± SD	Median (range)
Height, cm	158±5.9	158 (140-173)
Weight, kg	80.5±16	80 (52-150)
BMI, kg/m^2	32.2±6.6	31 (21-62)
Albumin, g/L	42.7±4.3	43 (27-51)
Hemoglobin, g/dL	12.3±1.7	12.4 (7.4-16.5)
Leukocyte count, x10^6/L	7288±2577.3	7020 (2950-23.380)
Neutrophil count, x10^6/L	4709±2161.2	4510 (1650-20.690)
Lymphocyte count, x10^6/L	1924±743	1760 (470-5090)
Operation duration, minutes	259.6±108.6	240 (90-680)
Number of RBC suspensions	0.2±0.7	0 (0-4)
Number of FFP units	0.1±0.4	0 (0-3)
ASA score	2.2±0.6	2 (1-4)
RL-RAM thickness, mm	7.9±2.2	7.85 (3.3-13.5)
RL-PMM thickness, mm	32.1±4.8	32.4 (20.8-42.8)

BMI: Body mass index, RBC: Red blood cell, FFP: Fresh frozen plasma, RL-RAM: Right-left rectus abdominis muscle, RL-PMM: Right-left psoas major muscle, ASA: American Society of Anesthesiologists, SD: Standard deviation

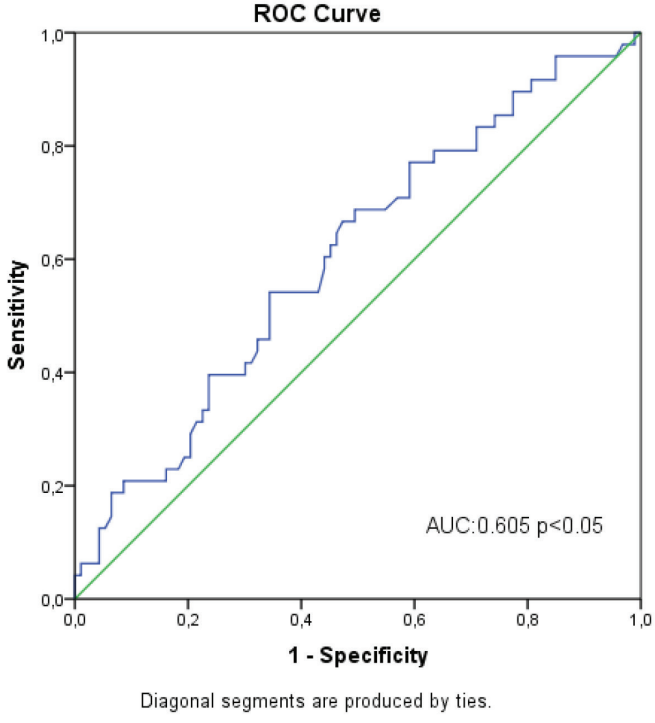

Figure 1. ROC curve for the average thickness values of right-left rectus abdominis muscle

ROC: Receiver operating characteristic

Table 3. Co-morbidity frequencies of the patients

Co-morbidity	n (%)
Hypertension	89 (63.1)
Diabetes mellitus	52 (36.9)
Malignancy (rectal cancer, breast cancer, colon cancer)	3 (2.1)
Schizophrenia	3 (2.1)
Asthma	10 (7.1)
Hypothyroidism	8 (5.7)
Coronary artery disease	5 (3.5)
Vertigo	3 (2.1)
Meningioma	1 (0.7)
Chronic obstructive pulmonary disease	5 (3.5)
Congestive heart failure	2 (1.4)
Hyperthyroidism	3 (2.1)
Sarcoidosis	1 (0.7)
Hyperlipidemia	4 (2.8)
Cerebrovascular disease	3 (2.4)
Heart valve disease	1 (0.7)
Parkinson's disease	1 (0.7)
Familial mediterranean fever	1 (0.7)
Mental retardation	1 (0.7)
Venous insufficiency	1 (0.7)
Rheumatic disease	1 (0.7)
Arrhythmia	1 (0.7)

p=0.039). When a threshold of 7.52 mm for RAM thickness was applied, the sensitivity was 54.2%, and the specificity was 65.6%. These values suggest that RAM thickness has a limited impact in predicting postoperative complications in patients treated surgically for endometrial cancer. Although RAM thickness above a specific value can predict morbidity risk, the multivariate analysis points to age and operation duration as independent risk factors for postoperative morbidity.

Studies highlighting the association between skeletal muscle mass and clinical outcomes in cancer cases have underscored the significance of the term sarcopenia (16,20). A meta-analysis examining the loss of muscle tissue and functionality due to aging, chronic diseases, and low physical activity has demonstrated that sarcopenia at diagnosis is associated with shorter survival in oncological patients (18). In research by Torres et al. (21), sarcopenia was found to be a strong predictor for survival in ovarian cancer when body composition was analyzed through CT scans. Seebacher et al. (22) suggest that preoperative sarcopenia is associated with shorter survival in patients treated with pelvic exenteration for recurrent gynecological malignancies. Although using a different measurement, consistent with our study, Wu et al. (23) found that low skeletal muscle mass in the PMM in hepatocellular carcinoma was a significant prognostic factor for overall and progression-free survival. However, low skeletal muscle mass in the RAM did not significantly predict oncological outcomes in their study (23).

Silva de Paula et al. (24) have reported that muscle quality was the most crucial predictive parameter for surgical complications and argued that understanding the impact of muscle quality on adverse outcomes in cancer patients could be a promising approach. Our presented study found that only RAM thickness could predict postoperative morbidity in univariate analysis; however, this effect did not persist in multivariate analysis. The measurement of PMM thickness was inadequate in predicting postoperative morbidity.

Advancing age can increase the risk of postoperative morbidity. Hag-Yahia et al. (25) have shown that age is an independent prognostic factor for predicting postoperative complications in endometrial cancer. Guy et al. (26) have found that perioperative

Table 4. Causes of postoperative morbidity

Causes of morbidity (n=48; 34%)	n	%
Non-surgical site infection	17	35.4
Surgical site infection	11	22.9
Chylous ascites	9	18.7
Atelectasia	5	10.4
Pulmonary thromboembolism	4	8.3
Cellulitis	1	2
Subcutaneous abscess	1	2
Intracranial hemorrhage	1	2
Psoas abscess	1	2
Splenic infarction	1	2
Pleural effusion	1	2
Two patients developed more than one morbidity		

Table 5. Factors related with postoperative morbidity

Parameters	Postoperative morbidity		p-value
	Developed	Did not develop	
Age, years	66.6±7.8	62.1±9.3	**0.005**
Height, cm	159.1±6.0	157.4±5.8	0.109
Weight, kg	79.8±15.7	80.9±16.2	0.680
BMI, kg/m^2	31.5±6.6	32.6±6.6	0.334
Albumin, g/L	42.3±4.4	43±4.2	0.397
Hemoglobin, g/dL	12.4±1.8	12.3±1.6	0.615
Leukocyte count, x10^6/L	7558.1±3223	7149.4±2178	0.374
Neutrophil count, x10^6/L	4915.3±2863.5	4584.8±1694.9	0.342
Lymphocyte count, x10^6/L	1894.8±671.3	1939.1±780.4	0.738
Operation duration, minute	287.9±114.7	245.1±103	**0.026**
Number of RBC suspensions, unit	0.13±0.5	0.24±0.7	0.341
Number of FFP, unit	0.13±0.5	0.07±0.4	0.440
ASA score	2.3±0.6	2.1±0.6	**0.038**
RL-RAM thickness, mm	7.4±2.1	8.2±2.1	**0.039**
RL-PMM thickness, mm	31.8±4.8	32.3±4.9	0.614

BMI: Body mass index, RBC: Red blood cell, FFP: Fresh frozen plasma, ASA: American Society of Anesthesiologists, RL-RAM: Right-left rectus abdominis muscle, RL-PMM: Right-left psoas major muscle, SD: Standard deviation

Table 6. The relationship between co-morbidity and pathological findings and postoperative morbidity

		Postoperative morbidity		p-value
		Parameter developed	Did not develop	
		n (%)	n (%)	
Hypertension	None	13 (25)	39 (75)	0.083
	Present	35 (39.3)	54 (60.7)	
Diabetes mellitus	None	29 (32.6)	60 (67.4)	0.633
	Present	19 (36.5)	33 (63.5)	
Tumor type	Endometrioid	29 (31.2)	64 (68.8)	0.263
	Non-endometrioid	20 (41.7)	28 (58.3)	
FIGO 2009 stage	I-II	27 (30.3)	62 (69.7)	0.150
	III-IV	22 (42.3)	30 (57.7)	

FIGO: International Federation of Gynecology and Obstetrics

Table 7. Multivariate model for predicting postoperative morbidity

Parameters	OR	95% CI	p-value
Age, years[1]	Reference	1.01-1.12	**0.033**
	1.06		
RL-RAM thickness, mm[2]	Reference	0.69-1.05	0.166
	0.86		
ASA score[1]	Reference	0.76-3.20	0.228
	1.54		
Operation duration, minute[1]	Reference	1.0003-1.007	**0.039**
	1.003		

[1]: Median value, [2]:A cut-off value of 7.52 mm was used for the multivariate analysis of the mean right-left rectus muscle thickness, CI: Confidence interval, ASA: American Society of Anesthesiologists, RL-RAM: Right-left rectus abdominis muscle

medical and surgical complication rates linearly increased with older age, hospital stays lengthened, and discharge rates decreased in their study examining surgery for endometrial cancer. Conversely, Mascarella et al. (27) observed that while modeling age as both a categorical and continuous variable, it alone did not sufficiently predict major postoperative adverse events compared to other perioperative variables. In our study, age was an independent prognostic factor determining postoperative morbidity within 3 months postoperatively, with each unit increase in age raising the morbidity rate by 1.06 times.

The duration of surgery is a significant factor in the success of surgical operations and the rapid recovery of patients. In a meta-analysis by Cheng et al. (28) examining the relationship between the duration of surgery and the risk of surgical site infection, they defined a direct proportional increase in surgical site infections with prolonged operation times, with each increment of 15, 30, and 60 minutes respectively increasing the rates of surgical site infections by 13%, 17%, and 37%. Mahdi et al. (29) demonstrated that surgeries lasting 15% longer than the average duration in obstetric and gynecologic procedures doubled the incidence of surgical site infections. In our study, we found that the duration of the operation is an independent predictor of postoperative morbidity. Specifically, we observed that for each unit increase in operation duration, there was a corresponding 1.003-fold increase in morbidity.

The ASA score is a measure used to classify patients' overall health status before surgery and has been directly linked to an increased risk of postoperative morbidity. Kastanis et al. (30) have demonstrated a direct relationship between higher ASA scores and increased postoperative morbidity, suggesting that higher scores correspond with increased morbidity rates. Bakkum-Gamez et al. (31) identified an ASA greater than 2 as a risk factor associated with superficial incisional surgical site infections. In our study, the ASA score was higher in the group that developed postoperative morbidity in univariate analysis; however, its effectiveness in predicting postoperative morbidity did not persist in multivariate analysis.

Obesity is associated with an increase in morbidity and mortality in the short and long term for surgical operations. Mahdi et al. (29), in their study examining the relationship between obesity and postoperative morbidity and mortality in endometrial cancer patients, found that morbidly obese patients mainly had higher rates of surgical and infectious postoperative complications. Smits et al. (32), in a study examining the impact of BMI on postoperative outcomes in ovarian cancer patients, showed that obesity increased wound complications and hospital stays but did not affect mortality. Conversely, our study did not find a significant relationship between BMI and postoperative morbidity.

Strengths of our study include the retrospective analysis of patients with endometrial cancer who underwent surgery via an elective laparotomy approach, the detailed evaluation of surgical procedures and preoperative preparations, and an adequate sample size of 141 patients compared to similar studies.

Study limitations

Due to the study's retrospective nature, potential limitations such as selection and information biases exist. Additionally, the inclusion of only patients meeting specific criteria may restrict the representation of the general population, affecting the general applicability of our findings due to the exclusion of patients undergoing minimally invasive surgical techniques or specific surgical procedures not being applied.

Conclusion

The study has identified age and operation duration as independent risk factors for predicting postoperative morbidity. However, a comprehensive assessment, including the thickness of RAM and ASA, could provide more definitive results. Particularly, preoperative RAM thickness evaluation could significantly contribute to postoperative risk management strategies. Conversely, our findings indicate that PMM thickness does not contribute to predicting postoperative morbidity risk. Consequently, this research highlights the need to consider multiple factors in assessing morbidity risk and underscores the importance of health status, age, RAM thickness, and operation duration. A holistic evaluation of these factors can be crucial in preparing patients for surgery and improving postoperative care plans.

Ethics

Ethics Committee Approval: *Ethical approval was granted by the Ethics Committee of Ankara Bilkent City Hospital (approval number: E2-23-4349, date: 19.07.2023).*

Informed Consent: *Retrospective study.*

Footnotes

Author Contributions: *Surgical and Medical Practices: H.B.R., T.A., F.K., T.T., Concept: F.K., T.T., Design: T.T., Data Collection or Processing: H.B.R., T.A., H.B., A.A.T., Analysis or Interpretation: H.B.R., T.A., O.A., Literature Search: H.B.R., H.B., O.A., A.A.T., T.T., Writing: H.B.R.,*

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Multiple sclerosis, urinary tract infections and infertility: a comprehensive scoping review

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Abstract

Multiple sclerosis (MS) is an autoimmune disease that involves the central nervous system. MS is prevalent among young adults and progressively destroys axons and myelin. Individuals with MS often experience complications, such as lower urinary tract dysfunction, urinary tract infections (UTIs) and sexual dysfunction. In young adults MS may cause sexual dysfunction and infertility, which worsens as the disease progresses. The available evidence from different studies (microbiological and clinical studies, retrieved from PubMed and Scopus databases) on possible microbial pathogens causing MS was reviewed. Lower urinary tract dysfunction, UTIs and sexual dysfunction were investigated in people with MS. Over the past two decades advances in MS treatment have significantly slowed disease progression and altered its natural history. However, UTI and sexual dysfunction continue to pose substantial challenges for affected patients. As there is a causal relationship between UTIs and corticosteroid use during outbreaks, awareness of essential complications of MS, such as UTIs and infertility, is crucial for prevention, early diagnosis, and adequate management. [J Turk Ger Gynecol Assoc. 2025; 26(2): 130-41]

Keywords: Multiple sclerosis, infertility, urinary tract infections, sexual dysfunction

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Introduction

Lower urinary tract and sexual dysfunction are common in individuals with neurological conditions, such as multiple sclerosis (MS) (1,2). The high prevalence of genital symptoms reflects the complex neural control of the lower urinary and genital tracts within the central and peripheral nervous systems (3). These issues significantly threaten quality of life and have gained increased attention among neurologists. The increased prevalence of these symptoms underlines the importance of evaluating the link between MS and related complications. Although, there is no consensus, numerous articles have shed light on the connection between MS, urinary tract infections (UTIs), and infertility.

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A higher prevalence of UTI is seen among patients with MS. This is primarily due to urinary dysfunction and impaired bladder evacuation. The severity of MS also seems to be a risk factor for UTI, which usually precedes MS relapse. UTI can also complicate disease progression and may even be the cause of severe outcomes. MS has been linked to a higher prevalence of sexual dysfunction, ranging in severity from pain to complete genital paresthesia and various other symptoms. These urinary symptoms may correlate with the spinal cord involvement of the disease. The complex relationship between sexual dysfunction and how it relates to the lower urinary tract and the gastrointestinal system is well understood and requires a multifaceted strategy to treat these symptoms.

Despite conflicting reports, some research has highlighted the increased prevalence of infertility in MS patients (4). Some articles further state that pregnancy may protect against MS and reduce disease symptoms (5). This is not surprising, as the change in sex hormone milieu during pregnancy is known to affect other autoimmune conditions, such as systemic lupus erythematosus, which worsens during pregnancy, and, rheumatoid arthritis, which improves during pregnancy and then relapses again after delivery.

In this paper, the issue of infertility from the perspective of MS will be discussed. This paper provides an overview of possible microbial pathogens that cause MS, an evaluation of individuals with MS who report UTI and infertility, and a comprehensive update on several recent advances that have revolutionized the treatment (Table 1). To achieve this aim, studies published within the last 20 years and retrieved from reputable databases, such as PubMed and Scopus, were reviewed and the findings synthesized.

An overview of multiple sclerosis

MS is a chronic neuroinflammatory disease characterized by demyelination and varying degrees of axonal loss. MS is reported to be the most common neurological disease, mainly affecting young women between the ages of 20 and 45 years (6), and it is approximately three times as likely to occur in women compared to men (7). The exact cause of MS is not known; however, genetic factors such as human leukocyte antigen (HLA) allotypes (e.g., HLA-DR2), environmental factors such as inadequate exposure to sunlight and decreased vitamin D (8,9), higher body mass index, smoking, and latent microbial infections that lead to myelin and axonal damage (10,11) have been implicated. When stimulants bind to myelin proteins, they trigger a complementary autoimmune response that causes oligodendrocyte destruction, neuronal injury, perivascular inflammation, and chemical alterations in the lipid composition of myelin (12). Lesions primarily occur in the white matter, optic nerves, spinal cord, and periventricular regions, leading to atrophic pillars with fibrosis. The characteristics that correlate with the location of each lesion are linked to the severity and clinical subtypes of the disease (13). The first clinical event in these cases can be optic neuritis, myelitis deficiency, or brain stem pattern (14). Increasing disease duration, higher degree of disability, and being a woman are independently associated with higher symptom levels as measured by the urogenital distress inventory (UDI-6). Participants with moderate disability had scores 11.6 points higher than participants with mild disability on the UDI-6, whereas participants with severe disability had scores 17.6 points significantly higher ($p<0.0001$) (15). In 70% of these cases, urinary symptoms are caused by functional and neurological deterioration (16). Moreover, studies have shown that more women with MS are diagnosed with infertility than women without MS (12).

Extensive research has focused on investigating and treating genitourinary problems in MS. Neurologists should address these conditions, especially since many of these problems can now be treated symptomatically. Appropriate and timely treatment can help prevent further complications and thus boost the general quality of life of individuals with MS.

Potential microbial pathogens causing multiple sclerosis

It has previously been proposed that infectious pathogens play a role in the pathophysiology of MS, leading to clinical manifestations of the disease in genetically susceptible individuals (8). However, despite decades of intense research, no particular pathogen has been proven to cause MS. This is due to the possibility that microbial infections may create autoreactive cells, and intermingling microorganisms are usually cleared by the time a clinical diagnosis is made. Moreover, MS patients and healthy people may produce antibodies or autoreactive T cells against particular infectious pathogens. The development of MS may also differ depending on the type of infectious agents identified suggesting that a deeper understanding of the entire genome of the microorganism may be necessary to understand the mechanisms at work. In addition, autoimmune responses can vary during the progression of the particular infection, as some microorganisms induce a strong autoimmune reaction. In contrast, in others, this autoimmune response is reduced by the production of regulatory cells (17). Furthermore, the diversity of the clinical subtypes of MS can be a confounding factor in associating infections with the causes of MS. For instance, infections may not directly initiate an autoimmune response but rather precipitate subclinical conditions of the autoimmune system, for example radiologically isolated syndrome, which later progress to clinical disease (18).

Table 1. The summary of most critical articles referred to in this query, along with the broad issue and the specific factor they investigated

Study (references)	Broad issue	Specific factor being examined	Population	Outcome	Statistical significance
Fingerman and Finkelstein (6)	MS demographics	Age parameters of MS	N/A	The most common neurological condition affecting adults between the ages of 20 and 45 is MS.	N/A
Fingerman and Finkelstein (6)	MS demographics	Gender parameters of MS	N/A	Women are three times more likely than men to be MS patients.	N/A
Munger et al. (9)	Risk factors for MS	Vitamin D	148 cases, 296 controls	For every 50 nmol/L rise in 25-hydroxyvitamin D levels in white people, the risk of MS decreased by 41%. For various races, both statistically significant and insignificant data have been presented.	p=0.04
Xu et al. (91)	Risk factors for MS	High BMI	952 cases vs. 743,596 controls	The risk of MS raised with each unit (kg/m^2) increase in BMI.	Hazard ratio and 95% confidence interval (CI): 1,034; 1,016-1,053
Antonovsky et al. (92)	Risk factors for MS	Smoking	241 cases vs. 964 controls	Before the age at onset, a significantly larger percentage of patients (in contrast with controls) smoked.	p=0.02
Ascherio and Munger (8)	Risk factors for MS	EBV infection	1,770 EBV + cases, 9 EBV - cases, 2,374 EBV + controls, 152 EBV - controls	Only EBV stands out as a predictable and significant risk factor among the infectious agents that have been suggested to be linked to MS.	p<0.000000001
Marrie et al. (15)	MS associated complications	Lower UTI	9,688 total responders to the questionnaire	According to a linear regression analysis, being a woman, having a more severe impairment, and having a more prolonged condition were all independently linked to having more symptoms as measured by the UDI-6. On the UDI-6, participants with moderate disabilities scored 11.6 points more than those with mild disabilities, and those with severe disabilities scored had 17.6 greater points.	p<0.0001
MacDonald et al. (89)	MS associated complications	Infections and MS	1,439 women with MS vs. 1,101,165 women as controls	An estimate for the cumulative incidence for infections during pregnancy is 57.7% and 43.4% for women who are not MS patients and for those who are, respectively. The most prevalent type of infections is found to be genitourinary infections.	95% CI: 1.16, 1.27

Table 1. Continued

Study (references)	Broad issue	Specific factor being examined	Population	Outcome	Statistical significance
Houtchens et al. (76)	MS associated complications	Infertility	96,937 women with MS vs. 96,937 women as controls	Compared to women without MS, a considerably higher percentage of women who are MS patients (8.5% vs. 8.1%) were diagnosed to be infertile.	p=0.0006
Houtchens et al. (76)	MS associated complications	Live birth rates	96,937 women with MS vs. 96,937 women as controls	Women with MS had a considerably reduced total live birth rate when contrasted with women without MS (5.0% vs. 7.0%).	p<0.0001
Fong et al. (79)	MS associated complications	Rates of cesarean sections in MS patients	1,185 MS births that were affected with MS vs. 4,424,049 total deliveries	The prevalence of cesarean deliveries was shown to be greater among pregnant women with MS.	p<0.001
Chen et al. (81)	MS associated complications	Rates of cesarean sections in MS patients	174 women with MS vs. 1,392 controls	MS patients were found to be more likely to undergo cesarean sections.	p=0.032
Jalkanen et al. (85)	MS associated complications	Need for artificial insemination	61 births from MS patients vs. 55,547 controls	Artificial insemination was more frequently required to initiate pregnancies among MS patients.	p=0.0009
Lamaita et al. (12)	MS associated hormonal alterations	AMH alterations	Meta-analysis of 16 articles	Smaller ovaries with fewer follicles and lower AMH levels were seen in patients with uncontrolled disease and also in those with active MS as well.	N/A
Thöne et al. (71)	MS associated hormonal alterations	AMH alterations	76 reproductive-age females with RRMS vs. 58 healthy controls	Women with relapsing remitting MS were found to have a considerably lower mean AMH level.	p<0.04
Nikseresht et al. (40)	MS associated hormonal alterations	UTI as a result of urinary problems that occur due to MS	7 MS patients	Individuals with UTIs had a considerably higher prevalence of urinary problems than individuals without UTIs (64.5% vs. 40%, respectively).	p=0.036
Grinsted et al. (70)	MS associated hormonal alterations	Prolactin, LH, FSH, total and free testosterone alterations	14 women with MS vs. 14 control women	Prolactin, LH, and FSH levels were considerably greater in MS patients.	p<0.05
Grinsted et al. (70)	MS associated hormonal alterations	Estrogen alterations	14 women with MS vs. 14 control women	The serum levels of oestrone sulphate was substantially lower in the MS patients.	p<0.01
Grinsted et al. (70)	MS associated hormonal alterations	Testosterone alterations in women	14 women with MS vs. 14 control women	Total and free testosterone concentrations were notably higher in MS patients.	p<0.01

Table 1. Continued

Study (references)	Broad issue	Specific factor being examined	Population	Outcome	Statistical significance
Falaschi et al. (73)	MS associated hormonal alterations	Testosterone alterations in women	76 women with MS vs. 50 control	According to a specific questionnaire, MS patients had a higher incidence of hyperandrogenism (greasy skin, acne, and hirsutism) when compared to controls. This finding was statistically significant.	p<0.05
Foster et al. (93)	MS associated hormonal alterations	Testosterone alterations in men	4 men with MS vs. lab references	Men who are multiple sclerosis patients had demonstrated reduced total testosterone levels.	p=0.002
Fong et al. (79)	MS associated risks	Risk of UTI in parturients with MS	1,185 MS births that were affected with MS vs. 4,424,049 total deliveries	UTI rates were observed to be more common in pregnant women with MS.	p=0.003
Jalkanen et al. (85)	MS associated risks	Risk of preterm delivery in MS patients	61 births from MS patients vs. 55,547 controls	MS patients did not pose a statistically significant risk of cesarean sections.	p=0.965
Jalkanen et al. (85)	MS associated risks	Risk of preterm delivery in MS patients	61 births from MS patients vs. 55,547 controls	MS patients did not pose a statistically significant risk of preterm deliveries.	p=0.800
Fong et al. (79)	MS associated risks	Risk of preterm delivery in MS patients	1,185 MS births that were affected with MS vs. 4,424,049 total deliveries	Unadjusted data for preterm delivery indicated a slightly higher risk in MS participants, however following statistical adjustment, this link was found to be non-significant.	p=0.007
Chen et al. (81)	MS associated risks	Risk of preterm delivery in MS patients	174 women with MS vs. 1,392 controls	Preterm birth rates were higher among mothers with MS.	p=0.001
Marrie et al. (52)	UTI associated complications	The prevalence of genitourinary sistem diseases as a cause for hospital admission	5,797 persons with MS vs. general population cohort of 28,769 persons	Diseases of the genitourinary system were the second most frequent cause of hospital admission in the MS population.	p<0.0001
Harding et al. (56)	UTI associated complications	The role of UTI in patient mortality	176 UTI-related MS patient deaths (8.2%) vs. 10,746 UTI related deaths irrespective of MS (1.4%)	Deaths attributed to MS were more likely to be caused by UTI compared to deaths without any reference to the disease.	p<0.002

MS: Multiple sclerosis, BMI: Body mass index, EBV: Epstein-Barr virus, UTI: Urinary tract infections, LH: Luteinizing hormone, FSH: Follicle-stimulating hormone, AMH: Anti-mullerian hormone, RRMS: Relapsing-remitting multiple sclerosis, UDI: Urogenital distress inventory, N/A: Not available

Despite this, pathogens linked to the emergence or exacerbation of MS includes bacteria, such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, Herpesviruses (Epstein-Barr virus and Herpesvirus 6), enterotoxins produced by *Staphylococcus aureus* that act as superantigens, and human endogenous retrovirus families (19). In addition, *Acanthamoeba castellanii* protozoa and Candida fungal infections have also been considered (20). The results of studies conducted on human and animal models to investigate the relationship of these different pathogens with the occurrence and/or aggravation of MS, along with effective pathways such as molecular mimicry, epitope expansion, and bystander activation, have been discussed. However, infection with some parasites, including worms (*Hymenolepis nana*, *Schistosoma mansoni*, *Fasciola hepatica*, *Ascaris lumbricoides*, *Trichuris trichiura*, *Enterobius vermicularis*, *Strongyloides stercolaris*), appears to be associated with the occurrence or aggravation of MS (21).

Acute recurrences of MS are often triggered by upper respiratory tract infections (URTIs) or UTIs. Sibley et al. (22) were the first to define a two-week and a five-week risk before and after the onset of infection, during which the disease activity increases, likely due to an increase in the susceptibility to the infection (23). In considerable agreement with these findings, other investigators have demonstrated that disease aggravations during the high-risk period are more likely (24), and lead to prolonged relapses of increased severity (23).

Correale et al. (25) also studied whether UTIs had a relevance and showed a heightened risk of relapse during systemic infections. Furthermore, they demonstrated in transwell vulnerable cell co-cultures that myelin antigens induced an increase in antigen-specific T cell line proliferation during relapse, which possibly comes into being via vulnerable non-specific mechanisms. In addition to the activation of myelin-specific autoreactive T cells, other mechanisms have been considered to explain the observed association between MS and infections, such as molecular mimicry, antigen-based vulnerable cell activation, and direct microbial effects on the central nervous system (25,26).

Toll-like receptors (TLRs) are key factors in the human innate immune system. TLRs signal the production of inflammatory cytokines and interferons in response to stimulation by microbial epitopes, which then trigger additional adaptive immune responses (27). TLR2 and its heterodimeric partners, TLR1 and TLR6, are expressed on naive human regulatory T cells (Tregs) compromised in MS, potentially hindering their regulatory function (28). The processes behind how infections affect the clinical exacerbations of MS and the disease's progression are still poorly understood.

Urogenital and sexual dysfunction in multiple sclerosis patients

Genital dysfunction is a common problem affecting people of all ages, societies, and races (29). Although it is not yet fully defined, lower urinary tract dysfunction is a potential threat to the health of individuals and may lead to serious outcomes from UTIs. Urinary and sexual dysfunction can also compromise psychological and socio-economic wellbeing of individuals with MS (30). Both urine storage and excretion may be affected by MS, for which a functional assessment can only be made via urodynamic testing. Although estimates vary among studies, frequency depends on the stage of disease progression. Goldstein et al. (31) found that 2% of people with MS report having lower urinary tract dysfunction as their first symptom.

Neurogenic bladder disease probably affects virtually all individuals with advanced MS. Urodynamic abnormalities were detected in 52% of urologically asymptomatic patients with a relatively short mean disease duration of 5 years (32). As the neurological disease progresses, the treatment of bladder dysfunction becomes more complicated due to worsening detrusor overactivity, ineffective bladder evacuation, intermittent UTIs, spasticity, reduced mobility, and, sometimes, cognitive impairment (33).

Since upper urinary tract dysfunction is rare and preventable with well-timed ultrasound imaging, early-stage diagnosis in an MS center by a neurologist and a specialized nurse is recommended. The most frequent symptoms indicative of lower urinary tract dysfunction in MS are polyuria, urinary retention, urinary urgency, nocturia, and incontinence (34,35). A detailed history, urinalysis, and post-voiding residual urine determination by ultrasound provide the necessary data to treat infections, incontinence, and urgency. Treatment options include anticholinergics, bladder training, and intermittent catheterization. The need for a referral to a urologist can be considered in cases where first-line treatment has not provided adequate improvement. Treatment in end-stage MS has not yet been adequately studied, but in these cases, a suprapubic catheter is the favored technique for bladder drainage.

Urinary tract infections in multiple sclerosis patients

The frequency of UTI and bacteriuria in MS cases is high, with rates of 90% and 74%, respectively (36). This is largely due to urinary dysfunction, which can lead to increased hospitalization and nursing home admissions (36,37). Bladder evacuation in MS cases is closely related to UTI (38). Due to urinary issues, MS cases are prone to urinary tract colonization and, as a result, UTIs (39,40). Neurogenic bladder infection risk factors include increased urinary stasis, high bladder pressure, bladder stones,

and catheters (41). In addition, elderly age group, past antibiotic use, and the severity of MS are all risk factors for UTI (42,43). UTI often precedes MS relapse, and intermittent UTI is associated with acute exacerbations and neurological progression of the disease (36). Furthermore, it can be challenging to diagnose UTI in MS cases due to pre-existing urinary issues, which can result in misdiagnosis (40).

The most common symptoms of UTI in MS patients are urine retention, nocturia, urinary urgency, polyuria, and incontinence. Moreover, UTI in these patients can complicate the disease, cause additional damage, and even lead to severe neurological deterioration. In an extensive study of 458 (91.4%) subjects with MS who reported lower urinary tract symptoms, 130 (28.4%) reported intermittent UTI based on microbiological confirmation of bacteriuria and pyuria (44). It should be noted that UTI frequently occurs alongside symptoms such as increased bladder sensation, urine incontinence, increased frequency, urinary urgency, burning, dysuria, and/or lower urinary tract discomfort in people with MS (44). Urinary infections also increase hospitalization and mortality rates in this group. Therefore, MS cases with positive urinalysis or urinary symptoms should receive disease-modifying treatments and corticosteroid therapy.

In the MS population specifically, bacteria responsible for UTI were: *Pseudomonas aeruginosa, Proteus mirabilis, Klebsiella pneumoniae, Escherichia coli*, beta-hemolytic *Streptococcus* B, and Coagulase-negative *Staphylococcus* (35,45,46). In a study of 146 cases with neurogenic bladder, Clark and Welk (47) examined the results of follow-up urine cultures from patients with at least two positive urine cultures in two years. Their findings showed that the most common organisms were *K. pneumoniae*, *P. aeruginosa*, and *E. coli*. According to other research, *E. coli* was isolated frequently (50%) in instances of neurogenic bladder, followed by *Acinetobacter* (15%), *P. aeruginosa* (15%), *E. faecalis* (6%), and mixed organism infections (41,48,49). Treatment of UTI should follow standard guidelines by determining the cause of infections and implementing preventative measures with intermittent infections, along with concurrent careful monitoring of bladder function and ultrasound (50,51).

Hospitalization and mortality rate from urinary tract infection in multiple sclerosis patients

In MS cases, UTIs are one of the top three most common reasons for hospitalization, accounting for 30-50% of hospitalizations (52). In a study of patients with neurogenic bladder, spinal cord injury, and MS, Manack et al. (53) discovered that 31% of cases had UTIs within a year of diagnosis, and 21% required hospitalization for UTIs. Furthermore, a link has been reported between a high "Extended Disability Status Scale" score and prolonged illness duration, which raises the risk of infection (54,55). UTIs have also been identified as a predictor of death in individuals with MS (43,54). Harding et al. (56) examined the causes of MS-related deaths in British Columbia, Canada, between 1986 and 2013 (56). They inspected mortality rates using the International Classification of Diseases and determined which conditions contributed the most to the death of MS cases. Compared to deaths not related to MS, those that were due to MS were more likely ($p<0.002$) to be caused by UTI. This underscores the importance of preventing and managing UTIs in individuals with MS to improve their overall health and reduce mortality risk.

Management of lower urinary tract symptoms

Urinalysis and symptoms should guide treatment in each group, whether in clinically stable cases or cases with relapsing MS. There is no evidence to suggest that antimicrobial treatment is clinically effective in cases of asymptomatic bacteriuria. The prevalence of drug-resistant bacteria may substantially increase due to treatment of asymptomatic bacteriuria. However, treatment is recommended in certain cases, such as pregnant women, patients presenting with intermittent acute UTI, before treatment of UTI, or in cases where immunosuppressive drugs are used. The activated immune response may be one possible reason of progressing disease and an otherwise stable situation worsening (57).

The use of corticosteroids is contraindicated in cases of UTI, as it prevents the patient from mounting an optimal immune response and increases the risk of progression into a systemic infection, which may become life-threatening due to complications (39,41). Steroid use can make infection control more challenging after starting the treatment regimen (58). If the patient has a UTI or bacteriuria, the current practice is to determine the presence of infection before starting treatment in acute relapse.

A case report by Tutuncu et al. (59) showed the association between MS exacerbations and UTIs. This study reported the development of severe dysarthria and diplopia alongside a new gadolinium-enhancing lesion preceded by the emergence of the disease. After treating the UTI, it was fully healed within two weeks. This can be achieved through careful history taking, bedside tests, and examination, including urine dipstick, a rapid and effective screening tool (60). This is useful in clinical situations where the use of steroid medication is essential to alleviate the symptoms associated with an acute relapse, thus minimizing short-term complications, which include both sensory or motor dysfunction of the patient.

When markers of infection are positive on a urine marker and the case is confirmed to have an acute relapse, it should be determined whether signs of systemic disease are present.

It is wise to use antibiotics to treat UTI and to use corticosteroids to reduce the recurrence of the patient's condition (39). This can promote lower levels of discomfort, greater satisfaction, less severity, and a shorter relapse period. To ensure safety, it is a priority to educate and advise the patient to call or return to the clinic if systemic symptoms, such as fever or convulsions occur (58).

Sexual dysfunction in multiple sclerosis patients

MS is linked to a higher prevalence of sexual dysfunction, regardless of gender. Men may experience dysfunction regarding erections and ejaculations. In contrast, women may experience decreased lubrication and genital hyper/hypo-sensitivity, which may even include complete anesthesia or hypoesthesia, and various types of pain (61). Most of these complications seem to be related to the involvement of the spinal cord in MS, typically associated with the lower extremities and urinary symptoms. As shown by magnetic resonance imaging in patients with relapsing-remitting multiple sclerosis, sexual dysfunction is also related to severe lesions in the pons (62). Clinical examination may not rule out neurogenic sexual dysfunction, but it can determine the scope of other MS-related deficits associated with sexual counseling, such as spasticity and loss of sensation.

Electrodiagnostic studies, including measurements of vibratory thresholds in the clitoris (63) and cortical evoked potentials of the dorsal clitoral nerve (64), imply that pudendal somatosensory input is essential for female orgasmic function, which may also be the case in early and mild MS. Depending on the clinical parameters of the analyzed samples and the follow-up time, sexual dysfunction occurs in 30% to 70% of cases (65). Among female patients with MS, the most common instances of sexual dysfunction are decreased libido (31-64%), decreased vaginal lubrication and sensation (33-52%), and anorgasmia (37-38%) (66). In men with MS, the most common instances of sexual dysfunction are decreased sexual desire (37-86%), erectile dysfunction (34-80%), decreased sensation (21-72%), ejaculatory dysfunction (34-61%), and difficulty reaching orgasm (29-64%) (67).

Bowel and bladder problems associated with MS can also affect sexual activity and interfere with intimate behavior and social relationships (68). Increased libido can also sometimes cause problems (69).

Studies show women with MS have reduced estrogen and higher follicle-stimulating hormone (FSH) and luteinizing hormone levels during the early follicular phase (70). Decreased ovarian reserve has been associated with higher FSH levels in the early follicular phase. Various different studies have reported an increased prevalence of hyperandrogenism and hyperprolactinemia in women with MS (55). In addition, reduced levels of anti-Mullerian hormone, a peptide hormone of the ovarian follicular pool and physiology, have been observed in women who have MS when contrasted with healthy women (71). Moreover, ovarian volume and antral follicle counts were decreased in MS patients using immunomodulating drugs (72). These alterations could explain why one of these studies demonstrated that there was a slight increase in the prevalence of oligo/amenorrhea in women with MS (16% in controls) (73). In men, decreased testosterone levels may affect sperm production, libido, and sexual function (74). However, good sperm production may be preserved despite abnormal testosterone levels (75).

Infertility in multiple sclerosis patients

Women with MS have been discouraged from getting pregnant for a long time due to worries about their ability to care for their children due to incapacity or fatigue (71). There is a significantly larger percentage of infertile women with MS than women without MS (8.5% vs. 8.1%; p=0.0006) (76). When stratified by age, the results showed that more women with MS between the ages of 18-34 years and 42 years and older had received a diagnosis of infertility when contrasted with women without MS (76). There is conflicting evidence about both the possibility of decreased fertility in MS patients and the impact of infertility treatment on the progression of MS. Likewise, it has been suggested that assisted reproductive technology increases the risk; however, there is insufficient evidence to confirm this claim (77).

Ashtari et al. (5) reported that MS has no effect on pregnancy outcomes, such as the number of miscarriages, ectopic pregnancies, stillbirths, and length of pregnancy, but it may also reduce the symptoms of the disease during the length of pregnancy. Thus, in their study, pregnancy had a protective role against MS. Despite the differences in male and female cases, overall, there is no conclusive evidence that women with MS experience fertility problems (4). Furthermore, infertility affects a large percentage of people who are of childbearing age, and thus MS may not always be the only cause. This issue should be discussed with MS patients, as some avoid pregnancy due to the fear of complications and lack of understanding regarding the use of medications in an appropriate safety class for pregnancy, and also the positive association between pregnancy and disease severity should be discussed. In addition, to ensure the greatest outcome for the mother and the fetus, it is important to counsel the patients regarding the most appropriate contraceptive methods, the best time to begin medical treatment, and the specific medication to use during pregnancy (12).

Perinatal outcomes in multiple sclerosis patients

As many pregnant women are MS patients (78-80), larger cohorts are expected to be studied to explore their risk for uncommon pregnancy complications. In some reviews, many (79-82), but not all (83-86), studies have reported higher rates of preterm delivery and Cesarean delivery among women with MS compared to women without MS. However, rarer complications, such as chorioamnionitis and postpartum hemorrhage, are not often considered (79). It is probable that women with MS have an increased risk of developing these complications due to a higher risk of prolonged labor and labor induction (83,86,87). Prior research investigating the likelihood of neonatal abnormalities in mothers with MS are generally in line in reporting an absence of increased risk, although sample sizes were limited (83,88). Moreover, many researchers have examined whether a more active disease had a correlation with increased risks of unfavorable pregnancy outcomes. The tendency for MS patients with milder disease to become pregnant contrasted with those who have comparatively more severe MS may ultimately lead to a lower risk of adverse pregnancy outcomes in women with MS. This may skew the data to demonstrate MS poses a lower-than-actual risk with regards to pregnancy outcomes. There is a critical knowledge gap in this area regarding the risks of adverse pregnancy outcomes in women with moderate to severe disabilities (86). According to one study, pregnant women with MS may be at a moderately increased risk of infection and premature delivery (89). Although the confidence intervals were broad and zero for all subtypes except genitourinary and respiratory infection subtypes, this study showed that women with MS had an increased risk of all infection subtypes except influenza.

Impact of multiple sclerosis treatment on infertility

In recent years, the treatment for MS has become more successful and has improved the quality of life, which has increased the willingness of parents to undergo successful infertility treatments. Therefore, couples should be managed in terms of the potential side effects of the medications used in the treatment of gonads, the impact of the disease on fertility, and the use of ovarian stimulation and its effect on MS. Published articles provide guidance on legal issues in situations where infertility treatments may adversely affect the progression of MS, as well as recommendations for how to treat infertility in MS patients. An interdisciplinary approach between neurologists and gynecologists is recommended to assess the risks and benefits of a particular procedure or treatment. For those who do not undergo MS infertility treatment due to MS-related medical conditions, they are advised to preserve gametes under the conditions prescribed by law (90).

The choice of treatment options for infertile couples with underlying neurological conditions depends on several factors. We need to determine whether the disease itself affects the reduction of ovarian reserve (DOR, a disorder that could result in infertility as the ovary loses its normal capacity for reproduction), and whether the medications used to treat the underlying disease are gonadotoxic. It is important to ensure that the underlying disease is not exacerbated by assisted reproductive techniques, and these procedures should be performed under optimal conditions. Any treatment of infertile couples with underlying conditions must be interdisciplinary and personalized, as the small number of these cases provides limited solid data in the literature on which we can base our decisions (90).

Conclusion

Neurological patients who report genitourinary symptoms require a comprehensive evaluation to plan a case-specific treatment approach. In addition, common URTIs, digestive tract, and genitourinary tract are also associated with MS exacerbations. Moreover, there seems to be a connection between the severity and course of the disease and various factors that may affect fertility. The limitations of this article are mainly due to the lack of research and consensus in certain topics, for example preterm delivery and the need for cesarean sections in pregnant women who have MS. Broader areas, such as fertility and how it is linked to the presence or severity of MS, has not been clearly shown in literature, although research suggest an association between the two. All in all, MS does not preclude the use of assisted reproductive technology in certain circumstances where it may be deemed necessary. Assisted reproductive technology does appear to be beneficial for conception in patients with MS, which is a supporting factor for the disease's association with infertility. Ultimately, MS should never be evaluated as an isolated neuropathy but rather be approached holistically. It may cause an extensive spectrum of complications, including infertility. Therefore, further research should be conducted to shed light on the relationships between MS and infertility, as well as with the latest techniques available for each stage or group of treatments used. Healthcare providers should always provide individualized care for their patients, especially regarding infertility, as it warrants additional investigation.

Footnotes

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Does geographical location impact the efficacy of oral antihypertensive therapy in pregnancy?

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Abstract

To assess the efficacy of anti-hypertensive medications during pregnancy according to race, ethnicity and geographical location as current evidence is not clear in this regard. A subgroup meta-analysis of randomized controlled trials was performed. The efficacy of oral medications for chronic hypertension in pregnancy by geographical location [United States of America (USA) vs. rest of the World] was investigated. The location was used as a surrogate of racial identification and differences in health care systems and availability of medications that might affect the efficacy of the treatment. The number of patients in each group experiencing the following outcomes: small for gestational age (SGA), preeclampsia, severe hypertension were compared. Seven studies were identified. Subgroup analysis revealed that medications did not affect the occurrence of SGA. In six studies, therapies were protective for preeclampsia in the rest of the world but not in USA (p=0.02). Therapies were protective for severe hypertension. Our findings suggest that location does not affect the efficacy of medication in treating chronic hypertension during pregnancy. Geographical location may serve as a surrogate for genetic characteristics of a population of interest. However, it can also be influenced by other factors such as the heterogeneity of populations such as the USA. (J Turk Ger Gynecol Assoc. 2025; 26(2): 142-53)

Keywords: Geographical location, hypertensive disorders of pregnancy, oral therapy, preeclampsia, pregnancy

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Introduction

Hypertensive disorders complicate approximately 10% of pregnancies worldwide with adverse maternal and fetal outcomes (1). Hypertension in pregnancy can be broadly categorized into four main conditions: chronic hypertension, gestational hypertension, preeclampsia, and eclampsia (2-4). Pharmacological management is traditionally based on beta blockers, calcium channel blockers and/or partial alpha blockers (1-3). In the case of non-pregnant women, there is a plethora of data, including randomized studies, showing the efficacy of antihypertensive agents in different racial groups (5,6). Using this extensive body of evidence, United Kingdom 2019 NICE guidelines (7) recommended when choosing antihypertensive drug treatment for adults of Black African or African-Caribbean family origin, an angiotensin II receptor

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blocker, in preference to an angiotensin-converting enzyme inhibitor. During pregnancy, non-Hispanic Blacks have a higher risk of pregnancy-induced hypertension and Asians/Pacific Islanders a lower risk of preeclampsia when compared to non-Hispanic White women (8).

A review from 2021 that included only randomized controlled trials (RCTs) in pregnant women, found only one trial that stratified outcomes of treated chronic hypertension by ethnicity (9). The only RCT that compared the use of oral nifedipine with labetalol for chronic hypertension during pregnancy according to the participants' ethnicity was published by Webster et al. (10). A total of 114 women with singleton pregnancies and a diagnosis of chronic hypertension were randomized to first-line antihypertensive therapy with either labetalol (n=56) or nifedipine (n=58). They found no difference in efficacy to reach the study's predetermined goal between the two medications overall and between Black and White individuals.

Given the availability of only one RCT in the literature on pregnant women regarding the efficacy of anti-hypertensive treatment during pregnancy according to ethnicity, we decided to use the location of the study as a surrogate for ethnicity of the patient. In addition, studying the effects of medical therapy according to geography allow us to factor in other influences towards the outcome, such as availability of health insurance for the general population, prevalence of comorbidities and other broad based baseline factors.

Material and Methods

We included RCTs on the efficacy of medications for chronic hypertension in pregnancy. We searched Medline, Embase, Scopus, Cochrane Library, the PROSPERO International Prospective Register of Systematic Reviews, and Google Scholar from July 20th, 1990, to July 20th, 2022.

We used the keywords "hypertension", "pregnancy", 'therapy" and "outcome". No language restrictions were applied. The references of related reviews and meta-analyses were searched manually. The following information was extracted from the complete manuscripts of the qualified studies: authors, location of the study, year of publication, number of patients treated with anti-hypertensive medication, and number of patients on placebo and/or aspirin. We divided the studies into subgroups according to the location of the study: United States of America (USA) vs. rest of the world. For each location the occurrence of outcomes were reported as follows: small for gestational age (SGA), preeclampsia, and severe hypertension. The definition of the outcomes are described in Table 1. These three outcomes were chosen based on clinical importance and because they were the most consistently collected outcomes in the included studies. For our analysis, patients on a different medication were considered to belong to a different study group.

Study selection

We included studies' medical therapy for the study group vs. placebo or aspirin in the control group. We excluded studies from which the data could not be extracted, such as case reports, reviews, meetings, letters, and surveys.

Data extraction

Two authors (B.M. and C.F.) conducted the study selection and independently screened the titles and abstracts to select potentially relevant citations for full text evaluation. When citations were considered relevant or when information in the title/abstract was insufficient for a decision on inclusion/exclusion criteria, the full text was retrieved and evaluated. In the event of discrepancies, a third reviewer was involved to help resolve conflicts and ensure accuracy.

Assessment of risk of bias

The risk of bias in each included study was assessed by using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (11,12). We used the risk-of-bias tool for randomized trials (Rob 2) tool structured into five domains of bias, according to the stages of a trial in which problems may arise: 1) the randomization process; 2) deviations from intended intervention; 3) missing outcome data; 4) measurement of the outcome; and 5) selection of the reported result (12). These categories were then used to assign an overall risk of bias for each of the articles considered in this meta-analysis. Review authors' judgments were categorized as "low-risk", "some concerns", or "high-risk" of bias. A proposed judgement about the risk of bias arising from each domain was generated. Two different authors assessed the risk of bias of all studies included in this review. In case of disagreement, a third reviewer adjudicated.

Statistical analysis

The data analysis was performed using Review Manager 5.4 (13) and R studio (14). Meta-analysis of adjusted and unadjusted risk ratios with 95% confidence intervals (CIs), using the Mantel-Haenszel method, was used to explore the association between anti-hypertensive therapy then pregnancy outcomes. A $p<0.05$ was considered statistically significant. We used the χ^2-based Cochran's Q test and Higgin'I^2 statistics to assess the degree of heterogeneity among studies. We considered an $I^2 \geq 50\%$ to be carrying considerable heterogeneity. If there was significant heterogeneity, the random-effects model was performed. Subgroup analyses were used to detect the contribution of each location (rest of the world vs. USA) to the outcome. In addition, we used the visualization of funnel plot and the relative Egger test to quantify the risk of publication bias. We considered an Egger test result with a $p>0.05$ as low risk of publication bias.

The institutional review board at the University of Arizona approved the study (approval number: STUDY00001570, date: 14.07.2022). We registered our protocol on PROSPERO, with registration number CRD42022348666, on August 8th, 2022.

Results

An initial search identified 3010 studies. However, out of these 3010 articles, only seven (0.2%) matched the inclusion and exclusion criteria.

Five studies were located in the "rest of the world" (15-19) and two studies were located in USA (20,21). All of them had data regarding SGA; six of them had data regarding preeclampsia and severe hypertension. We listed their definition of the outcomes and our interpretation for our analysis in Table 1, regarding each individual study.

Butters and Steyn (18) defined preeclampsia and severe hypertension according to the ISSHP criteria of 1988 (22) and they did not list the outcome severe preeclampsia.

Sibai et al. (20) did not specify the definition of preeclampsia, superimposed preeclampsia, and SGA; therefore, in our calculations, we interpreted their category term "superimposed preeclampsia" as belonging to our "preeclampsia" group, and their category "need for additional drugs to control severe hypertension" as belonging to the "severe hypertension group".

Tita et al. (21) defined preeclampsia and severe preeclampsia according to the American College of Obstetricians and Gynecologists (ACOG) criteria and referenced the ACOG

Table 1. Definitions of outcomes in the single studies

Authors, year, location	Definition of SGA	Definition of mild preeclampsia	Definition of severe preeclampsia	Definition of severe hypertension
Butters et al. (18)	BW <10th percentile	Data not present	Data not present	Data not present
Steyn et al. (19)	BW <10th percentile	ISSHP criteria of 1988*	Data not present	ISSHP criteria of 1988**
Vigil-De Gracia et al. (17)	BW <10th percentile	Data not present	New onset proteinuria with BP ≥160 mmHg systolic or ≥110 mmHg diastolic, or symptoms suggesting significant end-organ involvement	BP ≥160 mmHg systolic or ≥110 mmHg diastolic
Salama et al. (15)	BW <10th percentile	New onset proteinuria after 20 weeks of gestation	Data not present	BP ≥160 mmHg systolic or ≥110 mmHg diastolic
Rezk et al. (16)	BW <10th percentile	New onset proteinuria after 20 weeks of gestation	Data not present	BP ≥160 mmHg systolic or ≥110 mmHg diastolic
Sibai et al. (20)	Data present but definition not clarified	Data present but definition not clarified (it is called "superimposed preeclampsia" without further specifications)	Data not present	"Need for additional drugs to control severe hypertension"
Tita et al. (21)	BW <10th percentile	ACOG task force on Hypertension from 2013. They described the number of patients with "non-severe preeclampsia"	ACOG task force on Hypertension from 2013. They described the number of patients with "preeclampsia with severe features"	Worsening chronic hypertension
		They described the number of patients with "any preeclampsia" which is what we considered in our study		

*ISSHP criteria of 1988 for preeclampsia: single diastolic blood pressure measurement of 110 mmHg or more, or two consecutive measurements of 90 mmHg or more, at least 4 hours apart, without inclusion of the initial diastolic blood pressure or any systolic blood pressure value. Proteinuria is deemed to be important if it is more than 300 mg per 24 hour or 2+ on dipstick. **ISSHP criteria of 1988 for hypertension: single diastolic blood pressure measurement of 120 mmHg or more, or 2 consecutive measurement of 110 mmHg or more at least 4 hours apart. BP: Blood pressure, BW: Birth weight, SGA: Small for gestational age, ISSHP: International Society for the Study of Hypertension in Pregnancy, ACOG: American College of Obstetricians and Gynecologists

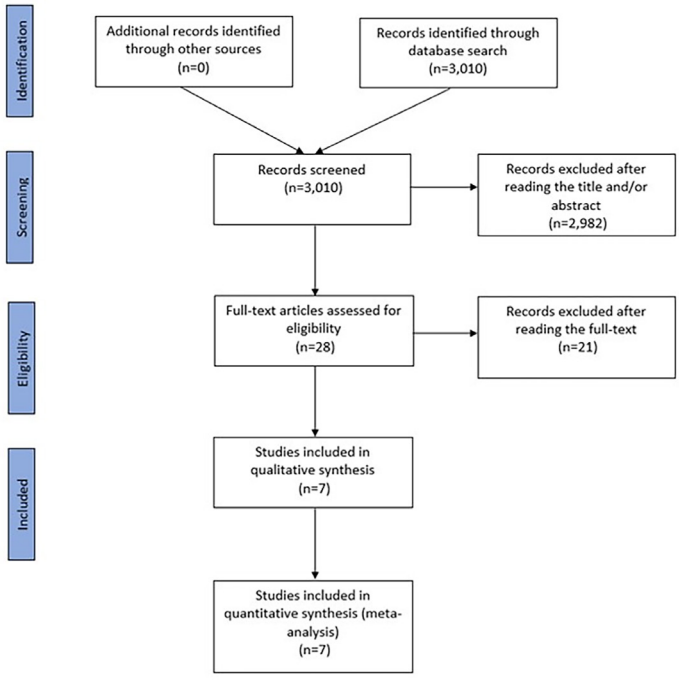


Figure 1. Flow chart of included/excluded studies

Table 2. Incidence of small for gestational age in the selected studies

Authors, year, location	Treatment type	Treatment (total)	SGA	No SGA	Comparator type	Comparator (total)	SGA	No SGA
Rest of the world								
Butters et al. (18)	Atenolol 50-200 mg daily	15	10	5	Placebo	14	0	14
Steyn et al. (19)	Ketanserin started at 40 mg per day % aspirin 75 mg per day*	69	7	62	Placebo + aspirin 75 mg per day**	69	9	60
Vigil-De Gracia et al. (17)	Amlodipine 5 mg a day	20	2	18	Aspirin 75 mg a day	19	2	17
	Furosemide 20 mg a day	21	1	20	Aspirin 75 mg a day	19	2	17
Salama et al. (15)	Methyldopa 1-2 gr per day + aspirin 81 mg per day	166	38	128	Placebo + aspirin 81 mg per day	164	32	132
	Nifedipine 20-40 mg per day + aspirin 81 mg per day	160	40	120	Placebo + aspirin 81 mg per day	164	32	132
Rezk et al. (16)	Labetalol 100-300 mg per day + aspirin 81 mg per day	160	66	94	Placebo + aspirin 81 mg per day	162	32	130
	Methyldopa 1-2 gr per day + aspirin 81 mg per day	164	34	130	Placebo + aspirin 81 mg per day	162	32	130
USA								
Sibai et al. (20)	Labetalol 300-2400 mg per day ± hydralazine 300 mg/day	86	7	79	Placebo	90	8	82
	Methyldopa 750 mg-4 gr per day ± hydralazine 300 mg/day	87	6	81	Placebo	90	8	82
Tita et al. (21)	Treatment (labetalol, nifedipine, amlodipine, methyldopa, HCTZ, other-data given only as aggregate)	1146	128	1018	Placebo	1124	117	1007

*Thirteen women in the ketanserin group needed additional antihypertensive medications - not specified which medications or outcomes for these. **Twenty-eight women in the placebo group needed additional antihypertensive medications - not specified which medications or outcome for these. SGA: Small for gestational age, USA: United States of America, HCTZ: Hydrochlorothiazide

task force on hypertension from 2013 (3); we grouped together the outcomes severe hypertension plus proteinuria, eclampsia, HELLP syndrome, and hypertension plus end-organ dysfunction. Moreover, they defined severe hypertension without preeclampsia as worsening chronic hypertension.

Regarding SGA there were 775 patients using anti-hypertensive medications and 773 patients using placebo/aspirin in the "rest of the world" group. In the USA group there were 1,319 patients using anti-hypertensive medications and 1,304 patients using placebo/aspirin Table 2.

Regarding mild preeclampsia in the "rest of the world" group, there were 760 patients using anti-hypertensive medications and 759 patients using placebo/aspirin, while in the USA group there were 1,381 patients using anti-hypertensive medications and 1,380 patients using placebo/aspirin Table 3.

The outcome of severe hypertension was reported for 760 patients using anti-hypertensive medications and 759 patients using placebo/aspirin in the "rest of the world" group. In the USA group 1,381 patients with severe hypertension using anti-hypertensive medications and 1,380 patients using placebo/aspirin Table 4.

The anti-hypertensive medications used were atenolol, ketanserin, amlodipine, furosemide, methyldopa, nifedipine, and labetalol. Tita et al. (21) did not specify exactly which medications they used, and have grouped several medications into one broad group.

Table 3. Incidence of preeclampsia in the selected studies

Authors, year, location	Treatment	Patient with antihypertensive drug	PE	No PE	Comparator type	Patients with no antihypertensive drug	PE	No PE
Rest of the world								
Steyn et al. (19)	Ketanserin started at 40 mg per day % aspirin 75 mg per day*	69	2	67	Placebo	69	13	56
Vigil-De Gracia et al. (17)	Amlodipine 5 mg a day	20	4	16	Aspirin	19	5	14
	Furosemide 20 mg a day	21	7	14	Aspirin	19	5	14
Salama et al. (15)	Methyldopa 1-2 gr per day + aspirin 81 mg per day	166	44	122	Placebo	164	80	84
	Nifedipine 20-40 mg per day + aspirin 81 mg per day	160	46	114	Placebo	164	80	84
Rezk et al. (16)	Labetalol 100-300 mg per day + aspirin 81 mg per day	160	48	112	Placebo	162	78	84
	Methyldopa 1-2 gr per day + aspirin 81 mg per day	164	50	114	Placebo	162	78	84
USA								
Sibai et al. (20)	Labetalol 300-2400 mg per day ± hydralazine 300 mg/day	86	14**	72	Placebo	90	14**	76
	Methyldopa 750 mg-4 gr per day ± hydralazine 300 mg/day	87	16**	71	Placebo	90	14**	76
Tita et al. (21)	Labetalol, nifedipine, amlodipine, methyldopa, HCTZ, others-data given only as aggregate	1208	295 (any preeclampsia)	913	Placebo	1200	373 (any preeclampsia)	827

*Thirteen women in the ketanserin group needed additional antihypertensive medications – not specified which medications or outcomes for these. **Their category term "superimposed PE" as belonging to our "PE" group. PE: Preeclampsia, USA: United States of America

Risk of bias of included studies

The "Rob 2" classification (12) showed that both studies had a low risk of bias (Table 5). The funnel plots are shown in Figures 3,4,6,7,9,10. The results of the Egger test (regression test for funnel plot asymmetry) were in accordance with the funnel plot "symmetry" and showed no evidence of publication bias.

Synthesis of results

Anti-hypertensives did not have any effect towards the occurrence of SGA in the US [relative risk (RR): 1.21, CI: 0.0.97-1.52] (Figure 2). Antihypertensives protected against preeclampsia in the rest of the world group (RR: 0.68, CI: 0.59-0.79) but not in the US where it did not reach statistical significance (RR: 0.85, CI: 0.67-1.09) (Figure 5).

Antihypertensives protected against the occurrence of severe hypertension (RR: 0.54, CI: 0.42-0.69) (Figure 8).

Discussion

Principal findings

Anti-hypertensive agents were not associated with an increased risk of SGA. In addition, they protected against preeclampsia and severe hypertension worldwide but not in the US where this effect did not reach statistical significance. We suggest that the reason why the USA differed in terms of preeclampsia is due to the year of the included studies (1990) which have likely biased the results-both studies from USA were done in 1990 while only 1 out of 5 studies from rest of the world was done in 1990-all the others were performed after 1990.

Comparisons with existing literature

Previous reviews and meta-analyses established the efficacy of antihypertensives during pregnancy but only one RCT by Webster et al. (23), analyzed the occurrence of poor pregnancy outcomes according to the ethnicity of the patient. They compared treatment with oral nifedipine and labetalol for chronic hypertension during pregnancy according to the participants' ethnicity. A total of 114 women with singleton pregnancies and a diagnosis of chronic hypertension were randomized to first-line anti-hypertensive therapy with either labetalol (n=56) or nifedipine (n=58). They found no difference in efficacy to reach the goal of the study between the two medications overall and between Black and White individuals.

Other meta-analyses were performed in regard of this topic earlier, but with key differences from our study. Bellos et al. (24) in 2020 included in the same analysis 22 RCTs and observational studies, while we included only RCTs. Particularly, they did not analyze the race/ethnicity of the patients. Al Khalaf et al. (25) performed a meta-analysis of 16 studies on anti-hypertensive treatment during pregnancy. They did not find any difference of interest regarding maternal race/ethnicity on pregnancy

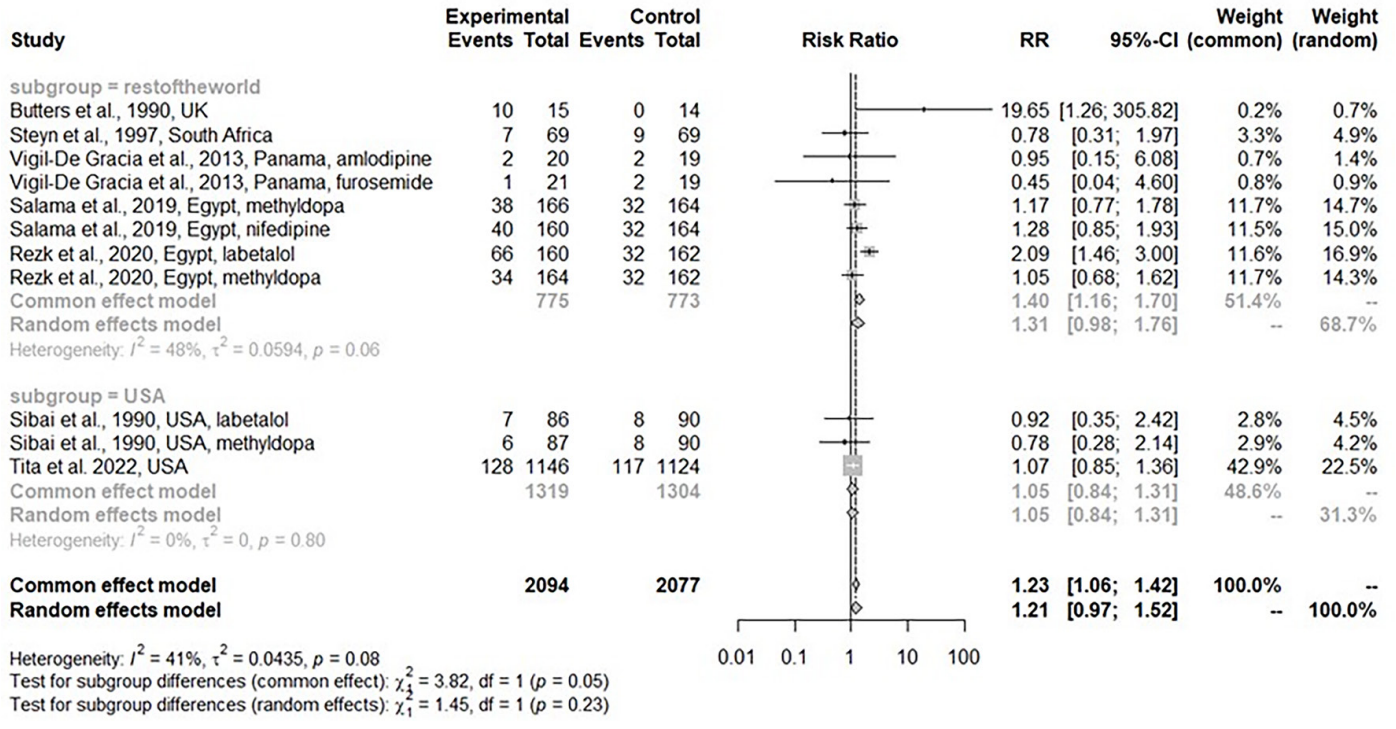


Figure 2. Forest plot of risk ratio of occurrence of small for gestational age via the meta-analytic method
RR: Risk ratio, CI: Confidence interval

outcomes. However, they included only observational studies while we included only RCTs. Bone et al. (26) performed a meta-analysis of 61 RCTs using oral antihypertensives for non-severe pregnancy hypertension, including all pregnancy hypertension types, while we focused only on chronic hypertension. They did not analyse the race/ethnicity of the patients.

Instead of dividing the patients per ethnicity, we divided the patients by location of the study.

In the present study factors other than ethnicity played a role, such as broader socio-economic determinants of health, including medical insurance coverage and comorbidities. The lack of difference in terms of outcomes in our subgroups for most of the included pathologies is similar to the results found

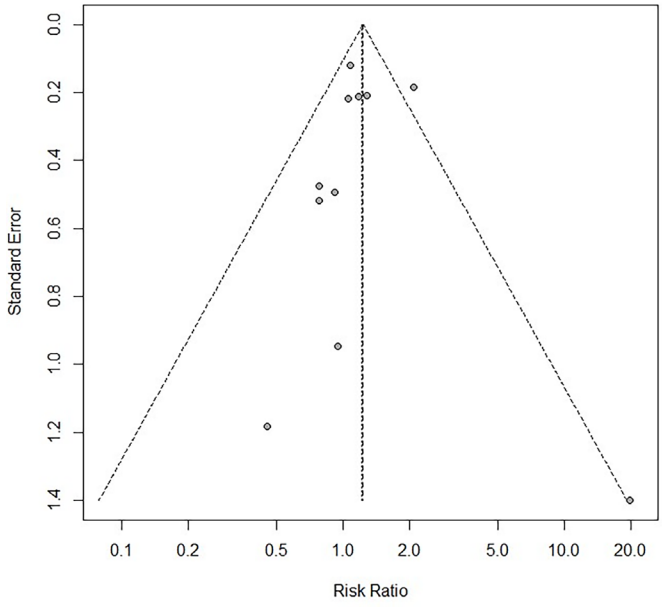


Figure 3. Funnel plot of standard error (symmetry/asymmetry risk of bias evaluation) considering small for gestational age as outcome

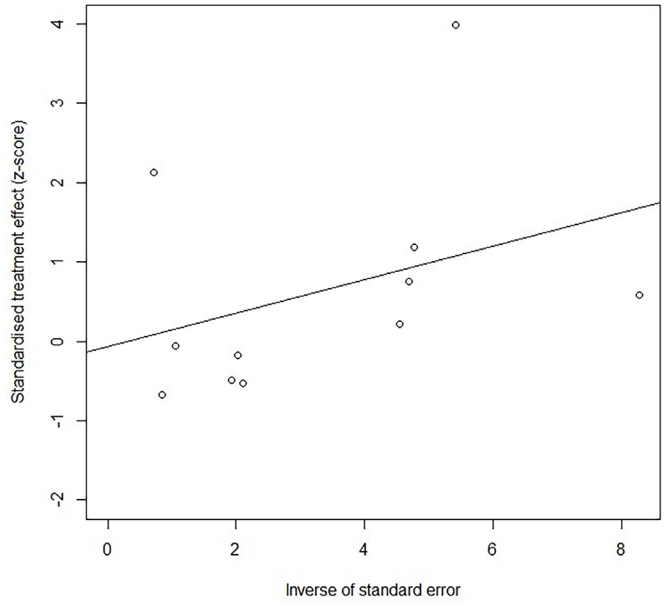


Figure 4. Linear regression test of funnel plot asymmetry for small for gestational age (p=0.9257, indicating no evidence of publication bias)

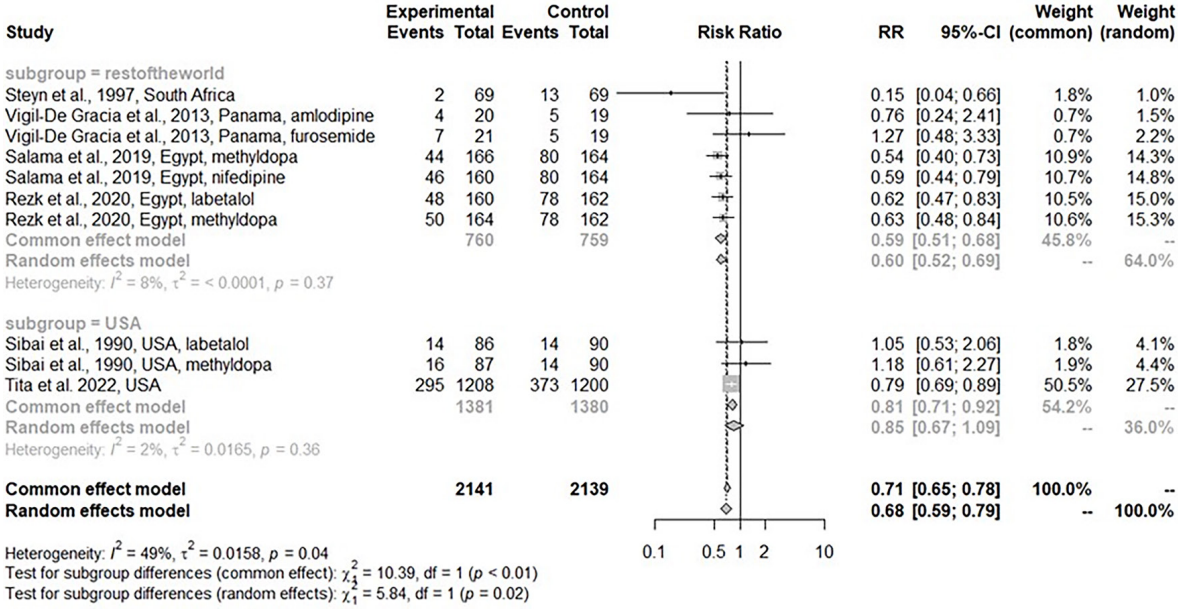


Figure 5. Forest plot of risk ratio of occurrence of preeclampsia via the meta-analytic method
RR: Risk ratio, CI: Confidence interval

by Webster et al. (27), pointing towards a hypothesis of equal efficacy of anti-hypertensive medications worldwide and in populations that are ethnically, socially and economically different.

Webster et al. (27) included RTCs published before November 2016, therefore excluding some more recent important large trials. They found 15 RCTs and they did not analyse the race/ethnicity of the patients. None of the previous studies stratified the outcomes based on the location of the study.

Study limitations

No previous study performed a subgroup analysis by location of the study. Our meta-analysis had strict inclusion criteria, including only RCTs and only women diagnosed with chronic hypertension. The limitations of the meta-analysis are the different drugs used and the high heterogeneity of the studies. In addition, the inclusion of studies from every year biased our study, indeed two out of seven studies were performed in the 1990s when the medications available and the health systems were drastically different from the present age (18,20).

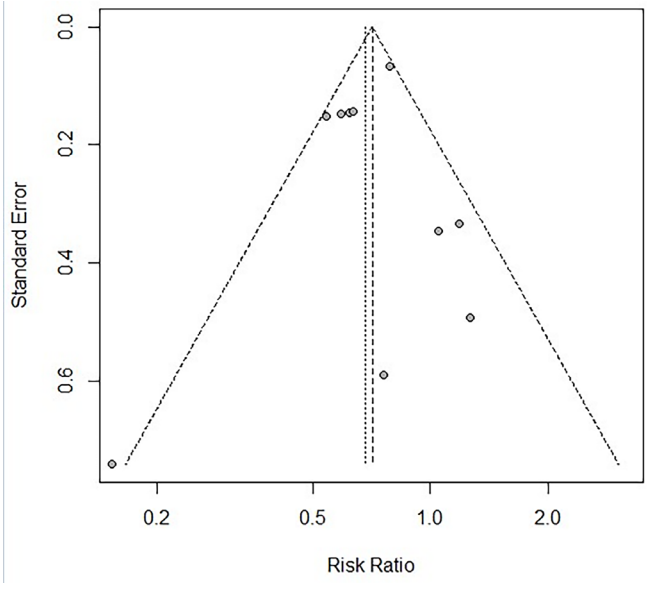


Figure 6. Funnel plot of standard error (symmetry/asymmetry risk of bias evaluation) considering preeclampsia as outcome

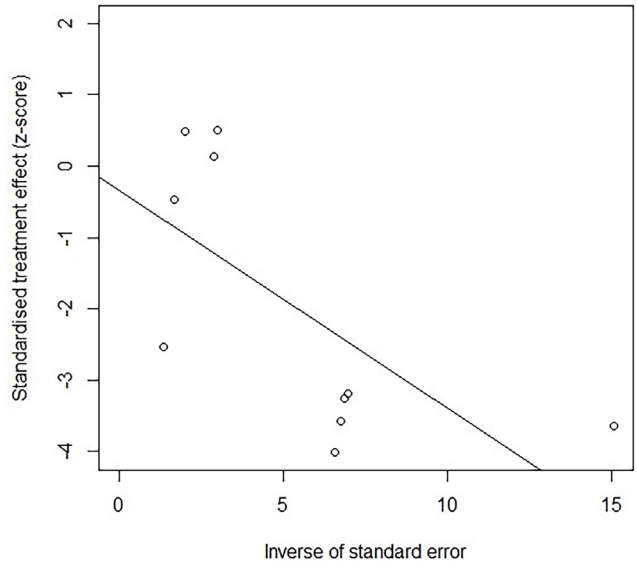


Figure 7. Linear regression test of funnel plot asymmetry for preeclampsia (p=0.6847, indicating low-risk of publication bias)

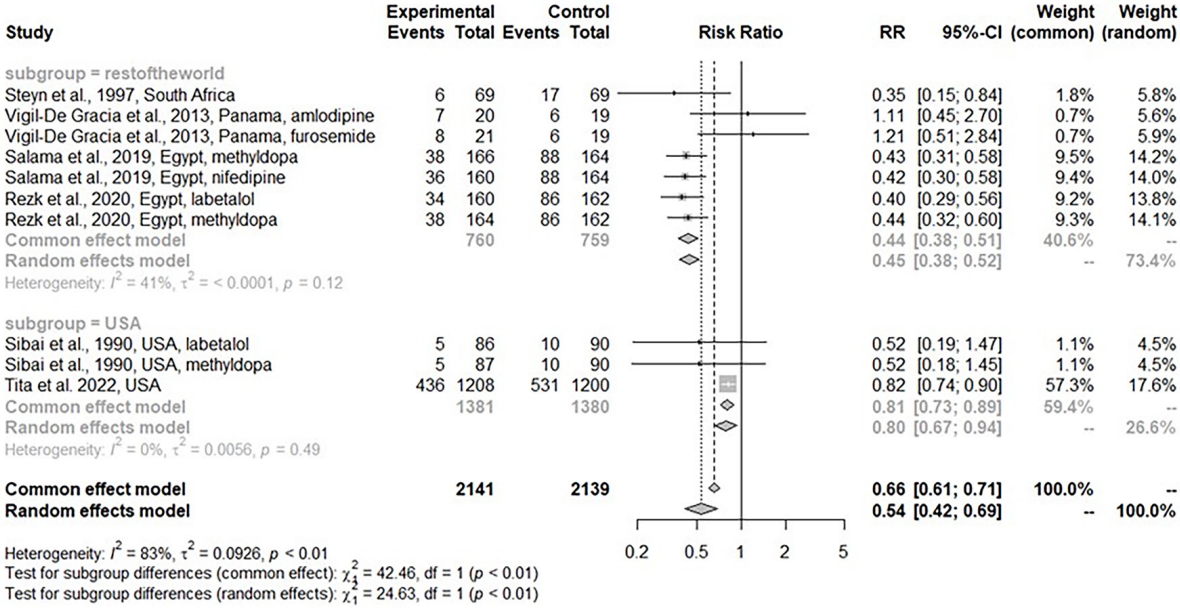


Figure 8. Forest plot of risk ratio of occurrence of severe hypertension via the meta-analytic method
RR: Risk ratio, CI: Confidence interval

Table 4. Incidence of severe hypertension in the selected studies

Authors, year, location	Treatment	Patient with antihypertensive drug	Severe hypertension	Non-severe hypertension	Comparator (type)	Patients with no antihypertensive drug	Severe hypertension	Non-severe hypertension
Rest of the world								
Steyn et al. (19)	Ketanserin started at 40 mg per day % aspirin 75 mg per day*	69	6 (severe hypertension ISSHP 1988)	63	Placebo	69	17 (severe hypertension ISSHP 1988)	52
Vigil-De Gracia et al. (17)	Amlodipine 5 mg a day	20	7	13	Aspirin	19	6	13
	Furosemide 20 mg a day	21	8	13	Aspirin	19	6	13
Salama et al. (15)	Methyldopa 1-2 gr per day + aspirin 81 mg per day	166	38	128	Placebo	164	88	76
	Nifedipine 20-40 mg per day + aspirin 81 mg per day	160	36	124	Placebo	164	88	76
Rezk et al. (16)	Labetalol 100-300 mg per day + aspirin 81 mg per day	160	34	126	Placebo	162	86	76
	Methyldopa 1-2 gr per day + aspirin 81 mg per day	164	38	126	Placebo	162	86	76
USA								
Sibai et al. (20)	Labetalol 300-2400 mg per day ± hydralazine 300 mg/ day	86	5**	81	Placebo	90	10**	80
	Methyldopa 750 mg-4 gr per day ± hydralazine 300 mg/day	87	5**	82	Placebo	90	10**	80
Tita et al. (21)	Treatment (labetalol, nifedipine, amlodipine, methyldopa, HCTZ, other - data given only as aggregate)	1208	436 (severe hypertension)	772	Placebo	1200	531 (severe hypertension)	669

*Thirteen women in the ketanserin group needed additional antihypertensive medications - not specified which medications or outcomes for these. **Need for additional drugs to control severe hypertension" as belonging to the "severe preeclampsia group". ISSHP: International Society for the Study of Hypertension in Pregnancy, HCTZ: Hydrochlorothiazide

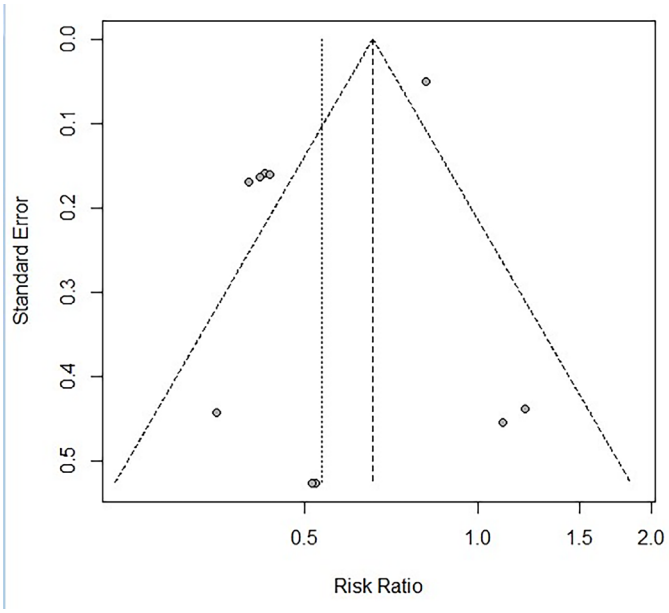


Figure 9. Funnel plot of standard error (symmetry/asymmetry risk of bias evaluation) considering severe hypertension as outcome

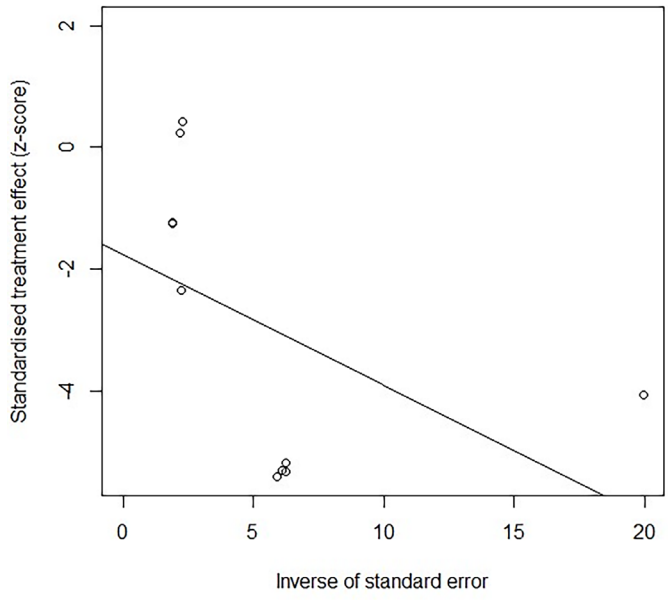
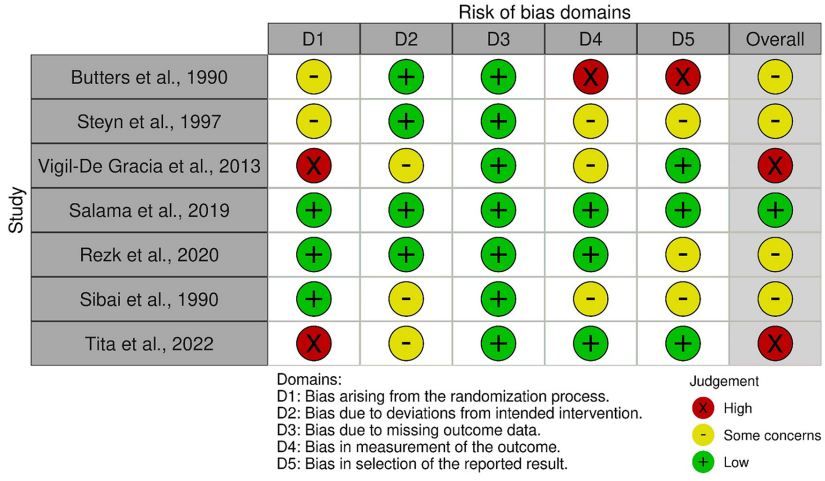


Figure 10. Linear regression test of funnel plot asymmetry for severe hypertension (p=0.1208, indicating no evidence of publication bias)



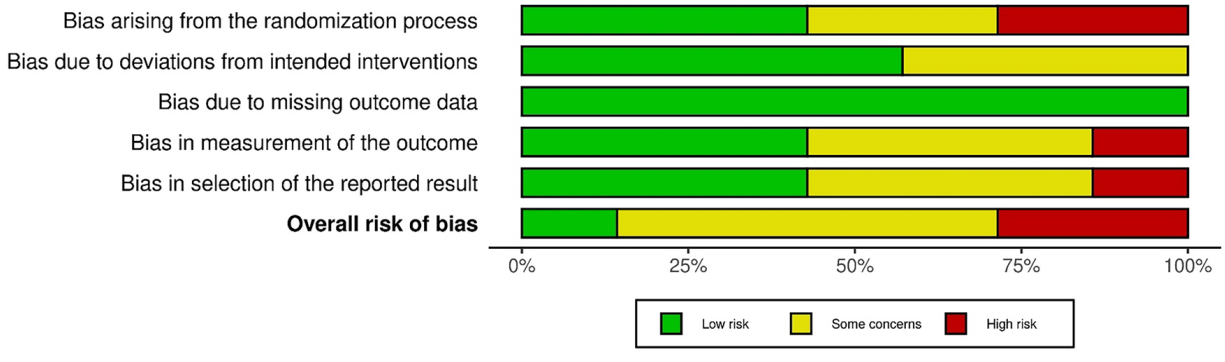


Table 5. Risk-of-bias tool for randomized trials (Rob) 2 assessment for selected studies.
D1: Bias arising from the randomization; process, D2: Bias due to deviations from the intended interventions, D3: Bias due to missing outcome data, D4: Bias in measurement of the outcome, D5: Bias in selection of the reported result

Conclusion

There seems to be no differences according to location, regarding the efficacy of medication in treating chronic hypertension during pregnancy. Geographical location could serve as a surrogate for genetic characteristics of a population of interest. However, it can be influenced by other factors such as heterogeneity of the ethnicity of the national population (e.g. USA), variation in healthcare systems and class of medications used (28,29).

We do not know how much of this is the result of the health system/availability of private vs. public insurance, ethnicity, and other baseline population characteristics. Therefore, we suggest conducting trials with outcome according to ethnicity and other baseline characteristics.

Footnotes

Author Contributions: *Design: A.S., G.S., Data Collection or Processing: B.A., C.F., Analysis or Interpretation: A.S., G.S., Literature Search: B.A., C.F., Writing: D.E., B.A., Critical Review: A.S., G.S., P.D.F.*

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What is your diagnosis?

A nulliparous female presented with the complaint of postcoital bleeding for one year. After each act of coitus, patient noticed minimal amount of fresh bleeding through vagina, accompanied by yellowish foul smelling discharge for the two months preceding attendance. As the couple was using condoms for contraception, there was staining of condom also with blood. The patient also had a history of anorexia and weight loss over the previous two months. The couple had been married for one year and were in a monogamous relationship. There was no history of any hormonal contraceptive use. However, she did not have a history of any cervical screening, nor had she had human papilloma virus (HIV) vaccination. Her menses were regular and there was no complaint of inter-menstrual bleeding. The patient didn't have any chronic cough or fever, nor there was any family history of tuberculosis.

On examination, body mass index was 18.1 kg/m^2 and she had mild pallor. She didn't have any abdominal mass and on per speculum examination, an irregular 3 cm x 3 cm ulcero-proliferative growth was seen over the cervix (Figure 1), which was friable and bled on touch. The external os could not be visualized as it was obscured by the growth. Colposcopy was performed which suggested a low grade lesion due to absence of acetowhite areas, however erosion of epithelium was noted. The uterus was anteverted, mobile and no adnexal mass or tenderness felt. The parametrium and rectal mucosa were free of growth or nodularity. A colposcopy guided cervical biopsy was taken followed by endometrial biopsy after locating the external os.

Answer

The cervical biopsy report showed multiple granuloma comprising of epithelioid histocytes surrounded by lymphocytes and Langhans multinucleated giant cells (Figure 2), however, staining for acid-fast bacilli was negative.

There was no evidence of malignancy and the endometrium was in the proliferative phase. Thus, the histopathology report suggested tuberculosis of the cervix. Pelvic ultrasound showed a normal sized uterus with normal endometrial thickness and adnexa without any free fluid in the pelvis. The serology for HIV and syphilis was negative. As the primary site of tuberculosis is almost always lungs, a chest x-ray was done, which was normal. A cartridge-based nucleic acid amplification test for *Mycobacterium tuberculosis* in the sputum sample was also negative. The patient was started on antitubercular therapy and there was marked improvement in her constitutional symptoms within one month of starting treatment. Postcoital bleeding stopped after two months of treatment and a repeat examination of the cervix also showed regression of the growth (Figure 3).

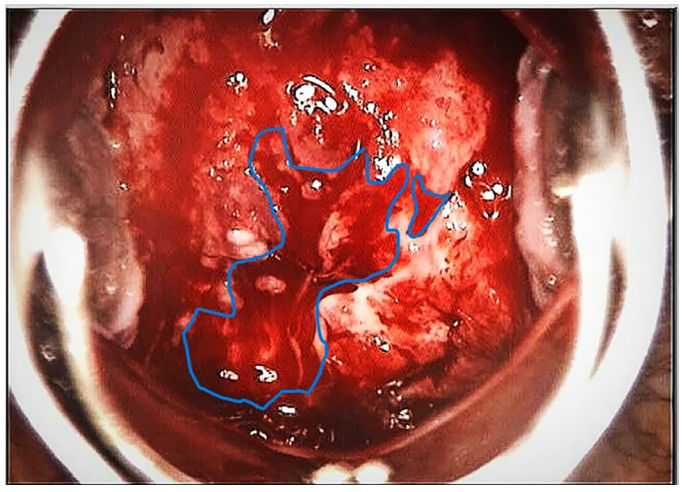

Figure 1. The ectocervix is replaced by an irregular ulceroproliferative growth. The denudation of cervical epithelium is marked by blue outline. The whole surface of cervix appeared friable and hyperemic

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She received therapy for a total of six months and was doing well on follow-up. A pap smear was done after completion of therapy, which was also normal.

The differential diagnosis of cervical growth in a young woman are (Table1).

The common sites of genital tuberculosis are fallopian tubes, endometrium and ovary. Vulva, vagina and cervix are rare sites of genital tuberculosis (1,2). The involvement of cervix alone without involvement of other genital organs is an extremely rare condition. The cervix can be involved with either a polypoidal growth, an ulcer or miliary tuberculosis (3). Although, the gold standard of diagnosis is the presence of acid-fast bacilli detected by either culture or staining by Ziehl-Neelsen or fluorescent stains, it is not always possible to demonstrate this, even in an active case of tuberculosis. In the present case, diagnosis was made on clinical examination which was confirmed by the presence of caseating granuloma, with lymphocytic and plasma cell infiltration on histopathology, which is pathognomonic of tuberculosis. Granulomatous lesions can be present even in sarcoidosis, lymphogranuloma venereum, amoebiasis, brucellosis, or foreign body granuloma but the specific histopathological changes suggestive of tuberculosis are caseating granulomas or tubercles surrounded by lympho-plasmacytic infiltration (4). A search was done in Pubmed using the terms “coital bleed” AND “tuberculosis”. Many similar cases of tuberculosis of cervix have been reported previously from developing countries, mainly from India (3,5-10). Most of these women were in their 20’s to 30’s and had history of postcoital bleed ranging from 3 months to 3 years. The antitubercular therapy includes an intensive phase for the first two months of treatment in which patient takes daily Rifampin, Isoniazid, Pyrazinamide, and Ethambutol. This is followed by a four-month course of continuation phase that consists of daily Isoniazid, Rifampin, and Ethambutol. Most of the women in previous case reports were given therapy for six months and one patient received it for nine months, possibly due to delayed response to the treatment (6).

Table 1. Differential diagnosis of cervical growth

Serial no.	Differential diagnosis	Description
1	Cervical carcinoma	It is unlikely at the age of 32 years, however, malignancy must be ruled out even at younger age. Although the maximum cases of cervical carcinoma in India are reported in the age group of 50 to 59 years, it can occur in young patients also. The only test to rule out malignancy is histopathology of the biopsy specimen.
2	Multiple warts	Cervical warts can be multiple and large enough to mimic growth. The typical appearance of wart is finger like projection over the surface.
3	Cervical tuberculosis	Tuberculosis is common in tropical countries like India, however, the cervix is a very rare site. It can mimic carcinoma of cervix on appearance. Histopathological diagnosis must be performed to differentiate between these.
4	Infected cervical fibroid polyp	Cervical polyps tend to occur as finger-like tissue growths. The majority of polyps are benign and are typically asymptomatic. After having intercourse or in between menstrual cycles, certain polyps result in bleeding. In rare cases, polyps can get infected and release a pus-like discharge from the vagina.

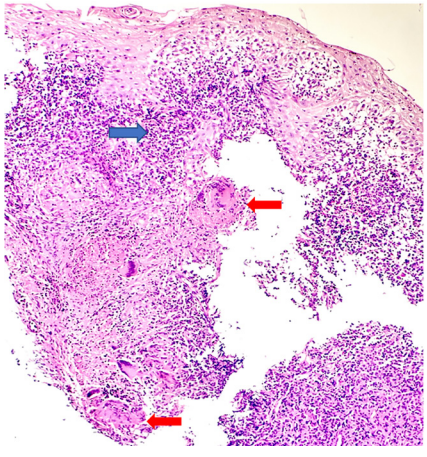

Figure 2. The histopathology stained specimen of cervix shows multiple caseating granulomas with Langhans cells (marked with red arrow) and lymphocytes and plasma cells infiltration of the stroma (marked by blue arrow)

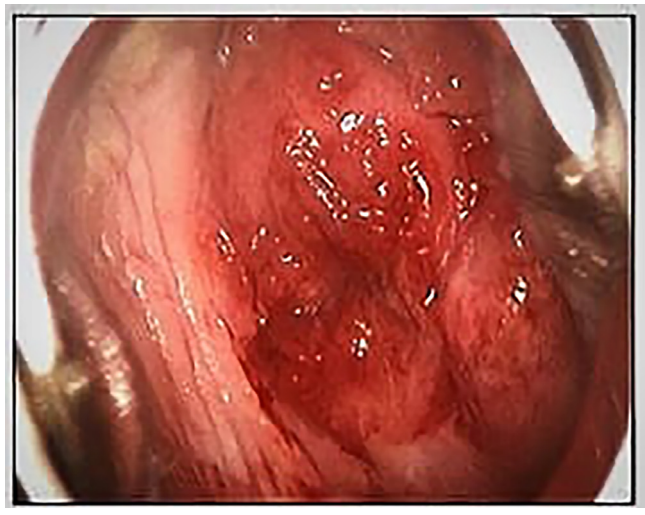

Figure 3. Regression of the growth over two months of antitubercular therapy

Take home message

- Postcoital bleeding is a symptom which should never be ignored and a comprehensive workup must be done.
- In a tropical country, tuberculosis must be ruled out in a young patient presenting with a cervical growth after ruling out malignancy.
- Response to antitubercular therapy must be monitored to rule out resistance.

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CONGRESS CALENDER

INTERNATIONAL MEETINGS

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

June 17-20, 2025	The Society of Obstetricians and Gynecologists of Canada Annual Clinical Scientific Conference, Whistler, BC, Canada
June 18-21, 2025	International Urogynecological Association (IUGA) 50th Annual Meeting, Barcelona, Spain
June 29-July 02, 2025	European Society of Human Reproduction and Embryology (ESHRE) 41st Annual Meeting, Paris, France
September 14-17, 2025	35th ISUOG World Congess, Cancun, Mexico
October 25-29, 2025	American Society for Reproductive Medicine (ASRM) 81st Annual Meeting, Texas, USA
October 19-22, 2025	ESGE 34th Annual Congress, İstanbul, Türkiye
November 08-11, 2025	The 54th American Association of Gynecologic Laparoscopists (AAGL) Global Congress on Minimally Invasive Gynecologic Surgery (MIGS), Vancouver, BC, Canada
November 27-29, 2025	The 33rd World Congress on Controversies in Obstetrics Gynecology & Infertility (COGI), Rome, Italy

CONGRESS CALENDER

NATIONAL MEETINGS

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

September 11-14, 2025	Uludağ Jinekolojik Endoskopi Kampı, Bursa, Türkiye
September 18-21, 2025	İç Anadolu Kadın Sağlığı Derneği Kongresi, Ankara, Türkiye
September 25-28, 2025	4. Tüp Bebek ve İnfertilite Derneği Kongresi, K.K.T.C.
October 01-05, 2025	7. Jinekoloji ve Obstetrikte Tartışmalı Konular Kongresi, Antalya, Türkiye
October 29-November 02, 2025	12. Üreme Tıbbı ve Cerrahisi Derneği Kongresi, Antalya, Türkiye
November 06-09, 2025	Uluslararası Jinekoloji ve Obstetri Kongresi (UJOK), Antalya, Türkiye
November 20-23, 2025	13. Üreme Sağlığı ve İnfertilite Kongresi, Antalya, Türkiye
February 12-15, 2026	8. Minimal İnvaziv Jinekolojik Cerrahi Kongresi, Ankara, Türkiye

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Answer form for the article titled “Multiple sclerosis, urinary tract infections and infertility: a comprehensive scoping review” within the scope of CME/CPD

1. **Which of the following is NOT mentioned as a risk factor for urinary tract infections in MS patients?**
   a. Increased urinary stasis and high bladder pressure
   b. Advanced age and previous antibiotic usage
   c. Severity of MS and presence of catheters
   d. Low body mass index and vitamin D deficiency

2. **What is the primary reason for the high prevalence of UTIs in individuals with MS?**
   a. Increased sexual activity
   b. Urinary dysfunction and impaired bladder evacuation
   c. Frequent use of corticosteroids
   d. Genetic predisposition to infections

3. **Why is the use of corticosteroids contraindicated in MS patients experiencing a UTI?**
   a. They directly damage the kidneys.
   b. They prevent an adequate immune response and increase the risk of systemic infection.
   c. They interact negatively with common antibiotics.
   d. They worsen bladder overactivity.

4. **Which of the following is identified as the MOST common manifestation of sexual dysfunction in women with MS?**
   a. Anorgasmia
   b. Decreased vaginal lubrication
   c. Genital pain
   d. Decreased libido

5. **What is the primary clinical tool recommended in the article for rapidly screening for UTI before initiating corticosteroid treatment for an MS relapse?**
   a. Blood culture
   b. Urine dipstick
   c. Renal ultrasound
   d. Bladder scan for residual volume

6. **Which bacterium is NOT mentioned as a common cause of UTI in MS patients?**
   a. *Escherichia coli*
   b. *Pseudomonas aeruginosa*
   c. *Staphylococcus aureus*
   d. *Klebsiella pneumoniae*

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1st Question

A	B	C	D

2nd Question

A	B	C	D

3rd Question

A	B	C	D

4th Question

A	B	C	D

5th Question

A	B	C	D

6th Question

A	B	C	D

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