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galenos yayınevi

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Turkish Journal of Obstetrics and Gynecology is the official peer-reviewed publication of the Turkish Society of Obstetrics and Gynecology and is published quarterly on March, June, September and December.

The target audience of Turkish Journal of Obstetrics and Gynecology includes gynecologists, obstetricians, urogynecologists, reproductive medicine specialists, gynecological oncologists and primary care physicians interested in gynecology practice. It publishes original work on all aspects of obstetrics and gynecology. The aim of Turkish Journal of Obstetrics and Gynecology is to publish high quality original research articles. In addition to research articles, reviews, editorials, letters to the editor and case presentations are also published.

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· Informed consent.

· Any explanations related to reporting guidelines.

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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/),

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

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Reports of animal experiments must state that the "Principles of laboratory animal care" (NIH publication No. 86-23, revised 1985) were followed, as well as specific national laws where applicable.

The editors reserve the right to reject manuscripts that do not comply with the above mentioned requirements. The author will be held responsible for false statements or for failure to fulfill the above mentioned requirements.

Authors must provide statement on the absence of conflict of interests between authors and provide authorship contributions and declare if any financial/metarial support.

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Title Page

A separate title page should list;

- The manuscript title, which should contain no more than a total of 100 characters (counting letters and spaces) and should not be declarative; do not use abbreviations or commercial names in the title.

- A short title of no more than 50 characters, including spaces, for use as a running foot.

- All author name(s), institutional, corporate, or commercial affiliations, and up to two major degree(s).

- Corresponding author's name, address, telephone (including the mobile phone number), fax numbers and e-mail address (the corresponding author will be responsible for all correspondence and other matters relating to the manuscript).

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The precis is a one-sentence synopsis of no more than 30 words that describes the basic findings of the article. Precis sample can be seen below:

'Using a 45 point questionnaire, we have evaluated the trend of Robotic surgery training in the gynecologic surgery fellowship programs across the nation'.

Abstract

All manuscripts should be accompanied by an abstract. All information in the abstract should be consistent with the information in the text, tables, or figures. Avoid use of commercial names in the abstract. Original research reports should have a structured abstract of no more than 250 words, using the following headings:

· **Objective:** Main question, objective, or hypothesis (single phrase starting with, for example, "To evaluate..." or "To estimate." [never start with "To determine."]).

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· **Material and Methods:** Study design, participants, outcome measures, and in the case of a negative study, statistical power.

· **Results:** Measurements expressed in absolute numbers and percentages, and when appropriate indicate relative risks or odds ratios with confidence intervals and level of statistical significance; any results contained in the abstract should also be presented in the body of the manuscript, tables, or figures.

· **Conclusion:** Directly supported by data, along with clinical implications.

Authors from Turkey or Turkish speaking countries are expected to submit a Turkish abstract including subheadings such as "Amaç, Gereç ve Yöntemler, Bulgular, Sonuç". The abstract of Authors whose native language is not Turkish will be provided free of charge translation services into Turkish language.

A structured abstract is not required with review articles and case reports.

Key Words

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

Turkish abstracts should have key words "Anahtar Kelimeler" picked from www.atifdizini.com under "Turkey Bilim Terimleri" link.

Several types of articles can be submitted for publication in Turkish Journal of Obstetrics and Gynecology: Original research, case reports, systematic reviews, current commentaries, procedures and instruments, and letters. Stated word counts and page limits were shown in Table 1.

Table 1. Manuscript length at a glance

Article type	Abstract Length	Manuscript Word Count*	Maximum Number of Authors	Maximum Number of References$^{\Phi}$
Original Research	250 words	5,500 words (~22 pages)$^{\Psi}$	NA	30
Case report	150 words	2,000 words (~8 pages)	4	8
Systematic review	300 words	6,250 words (~25 pages)	4	60
Current commentary	250 words	3,000 words (~12 pages)	4	12
Procedure and Instruments	200 words	2,000 words (~8 pages)	4	10
Letters	NA	350 words	4	5

*Manuscript length includes all pages in a manuscript (ie, title page, abstract, text, references, tables, boxes, figure legends, and appendixes). $^{\Phi}$Suggested limit. $^{\Psi}$The Introduction should not exceed 250 words. ~approximately; NA, not applicable.

Copyright transfer forms, the cover letter, and figures do not contribute to the page limits.

Original researches should have the following sections;

Introduction

State concisely the purpose and rationale for the study and cite only the most pertinent references as background. Avoid a detailed literature review in this section.

Material and Methods

Describe the research methodology (the patients, experimental animals, material and controls, the methods and procedures utilized, and the statistical method(s) employed) in sufficient detail so that others could duplicate the work. Identify methods of statistical analysis and when appropriate, state the basis (including alpha and beta error estimates) for their selection. Cite any statistical software programs used in the text. Express p values to no more than two decimal places. Indicate your study's power to detect statistical difference.

Address "IRB" issues and participants informed consent as stated above, the complete name of the IRB should be provided in the manuscript. State the generic names of the drugs with the name and country of the manufactures.

Results

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. Authors should report outcome data as both absolute and relative effects since information presented this way is much more useful for clinicians. Actual numbers and percentages should be given in addition to odds ratios or relative risk. When appropriate, number needed to treat for benefits (NNTb) or harm (NNTh) should be supplied. Emphasize only your important observations; do not compare your observations with those of others. Such comparisons and comments are reserved for the discussion section.

Discussion

Begin with a description of what your study found in relation to the purpose or objectives as stated in the Introduction. State the importance and significance of your findings to clinicians and actual patient care but do not repeat the details given in the Results section. Limit your opinions to those strictly indicated by the facts in your report. Compare your finding with previous studies with explanations in cases where they differ, although a complete review of the literature is not necessary.

Study Limitations

Provide information on the limitations of the study. No new data are to be presented in this section. A final summary is not necessary, as this information should be provided in the abstract and the first paragraph of the Discussion. Although topics that require future research can be mentioned, it is unnecessary to state, "Further research is needed."

Conclusion

The conclusion of the study should be highlighted. The study's new and important findings should be highlighted and interpreted.

Conflict of Interest

Authors must indicate whether or not they have a financial relationship with the organization that sponsored the research.

The main text of case reports should be structured with the following subheadings: Introduction, Case Presentation, Discussion, Study Limitations, Conclusion and References.

References

References are numbered (Arabic numerals) consecutively in the order in which they appear in the text (note that references should

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not appear in the abstract) and listed double-spaced at the end of the manuscript. The preferred method for identifying citations in the text is using within parentheses. Use the form of the "Uniform Requirements for Manuscripts" (http://www.icmje.org/about-icmje/faqs/icmje-recommendations/). If number of authors exceeds seven, list first 6 authors followed by et al.

Use references found published in peer-reviewed publications that are generally accessible. Unpublished data, personal communications, statistical programs, papers presented at meetings and symposia, abstracts, letters, and manuscripts submitted for publication cannot be listed in the references. Papers accepted by peer-reviewed publications but not yet published ("in press") are not acceptable as references.

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Examples

Journals; Zeyneloglu HB, Onalan G. Remedies for recurrent implantation failure. Semin Reprod Med 2014;32:297-305.

Book chapter; Ayhan A, Yenen MC, Dede M, Dursun P, Gultekin M.How to Manage Pre-Invasive Cervical Diseases? An Overview. In: Ayhan A, Gultekin M, Dursun P, editors. Textbook of Gyneaecological Oncology. Ankara, Turkey: Gunes Publishing; 2010.p 28-32.

Book; Arici A; Seli E. In Arici A and Seli E (edts). Non-invasive Management of Gynecologic Disorders. London: Informa Healthcare; 2008.

Tables and Figures

Tables should be included in the main document after the reference list. Color figures or gray-scale images must be at minimum 300 DPI resolutions. Figures should be submitted in "*.tiff", "*.jpg" or "*.pdf" format and should not be embedded in the main document. Tables and figures consecutively in the order they are referred to within the main text. Each table must have a title indicating the purpose or content of the table. Do not use internal horizontal and vertical rules. Place explanatory matter in footnotes, not in the heading. Explain all abbreviations used in each table in footnotes. Each figure must have an accompanying descriptive legend defining abbreviations or symbols found in the figure. If photographs of people are used, the subjects must be unidentifiable and the subjects must have provided written permission to use the photograph. There is no charge for color illustrations.

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Revisions will be sent to the corresponding author. Revisions must be returned as quickly as possible in order not to delay publication. Deadline for the return of revisions is 30 days. The editorial board retains the right to decline manuscripts from review if authors' response delays beyond 30 days. All reviewers' comments should be addressed a revision note containing the author's responses to the reviewers' comments should be submitted with the revised manuscript. An annotated copy of the main document should be submitted with revisions. The Editors have the right to withdraw or retract the paper from the scientific literature in case of proven allegations of misconduct.

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CONTENTS

LETTER FROM THE PRESIDENT

Dear Colleagues,

As you are all aware I have been elected a president of TSOG for the next two years.

First of all I would like to take this opportunity to thank you all.

During my presidency my first job will be to try to improve working conditions (including retirement payment) and to abolish compensation payment during vaginal births.

As you know this EBCOG Congress will take place between 17 and 21 May 2017 in Antalya. We hope to see all of you there for what should be on excellent congress.

The EBCOG board examination will be held in this congress for anyone who wishes to enter. It is a good opportunity for our young colleagues.

We invite you to contribute your papers to our journal in order to be accepted to SCI. We aim to succeed during this period with your valuable support.

Let me also take this opportunity to thank Prof. Dr. Eray Çalışkan for all his efforts. I look forward to working with him in the future.

In order to achieve our aims I have no doubt that all members of the TSOG will give their full support.

I hope to see you all in May at the EBCOG Congress in Antalya.

Best wishes

Ateş Karateke, Prof. MD

President of TSOG

TURKISH JOURNAL OF OBSTETRICS AND GYNECOLOGY

EDITORIAL

Dear Colleques,

In this last issue we have revised some of our Editorial Board. We would like to welcome our new coming colleagues and thanks to the others whom served well until now. As we have previously announced the Editorial Board will be renewed according to the time and effort spent for journal processing.

We will apply to be indexed by PubMed in 2017. We look for your continuing support in our scientific race in 2017 opinions of Turkish Society of Obstetrics and Gynecology will be published also in our journal on several malpractice cases such as postpartum hemorrhage, termination of pregnancy or menstrual regulation, cerebral palsy, shoulder dystocia and cesarean section. We hope to establish a scientific background for both management of these cases and hoping to prevent unnecessary patient claims and suits. I would also like to thank to all scientists that published their manuscripts in our journal and those reviewers who spent their valuable time for evaluating them. Our acceptance rate among the submitted manuscripts in 2016 was 54%.

I hope 2017 will bring us more scientific advancement.

Happy New Year.

Eray Çalışkan, Editor

Clinical Investigation / Araştırma

DOI: 10.4274/tjod.17047

Turk J Obstet Gynecol 2016;13:167-71

Evaluation of sleep disorder and its effect on sexual dysfunction in patients with Fibromyalgia syndrome

Fibromiyalji sendromlu hastalarda uyku bozukluğu ve seksüel disfonksiyona etkisinin değerlendirilmesi

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Abstract

Objective: Sexual problems are commonly seen in women with fibromyalgia syndrome (FMS). The objective of this study was to reveal the relationship between the severity of symptoms, sleep disorder, and sexual dysfunction in women with FMS.

Materials and Methods: A total of 140 sexually active women with FMS aged 17-67 years who presented to our physical medicine and rehabilitation outpatient clinic between January 2016 and June 2016 were enrolled in the study. The patients' age, height, body weight, body mass index (BMI), and general pain score [visual analogue scale, (VAS)] for the last 1 week were recorded. The patients were given three different sets of questionnaires: the Pittsburgh Sleep Quality Index (PSQI), Fibromyalgia Impact Questionnaire (FIQ), and Female Sexual Function Index (FSFI).

Results: The mean age of the patients was 40.3±8.5 years; the mean BMI was 27.1±4.4 kg/m^2, VAS (last 1 week) was 6.9±2 cm, the mean PSQI was 24.8±10.8 (one patient with PSQI ≤5), FIQ was 65.9±19.2, and FSFI was 19.0±6.9. No significant relationship was observed between the mean PSQI and BMI values (p=0.401), whereas a significant relationship was found between the mean values of VAS, FIQ, and FSFI (p=0.03; p=0.034; p<0.001, respectively). In Pearson's correlation analysis, a positive correlation was noted between PSQI and VAS (r=0.324; p<0.001) and FIQ values (r=0.271; p=0.001). A significant relationship was found between the FIQ and VAS values (p<0.001). P less than 0.005 was considered statistically significant.

Conclusion: Sleep disorder is regarded as the underlying cause for many signs and symptoms in FMS. Sexual dysfunction may develop in women with FMS, based on the severity of the disease and poor sleep quality. We found that sleep dysfunction was significantly related with the severity of disease, pain, and sexual disfunction. We also found a positive correlation between VAS and PSQI.

Keywords: Fibromyalgia syndrome, sexual dysfunction, sleep disorder

Öz

Amaç: Fibromiyalji sendromlu (FMS) kadınlarda seksüel disfonksiyona sık rastlanmaktadır. Burada FMS kadınlarda semptomların ciddiyeti, uyku bozukluğu ve cinsel fonksiyon arasındaki ilişkiyi ortaya koymayı amaçladık.

Gereç ve Yöntemler: Çalışmamıza Ocak 2016-Haziran 2016 tarihleri arasında fiziksel tıp ve rehabilitasyon ayaktan hasta polikliniğine başvuran 17-67 yaş aralığında cinsel aktif 140 FMS'li kadın hasta dahil edildi. Hastaların yaş, boy, kilo, vücut kitle indeksi (VKİ), son 1 haftalık genel ağrı skoru (VAS) kayıt edildi. Hastalara Pittsburg Uyku Anketi (PSQI), Fibromiyalji Etki Anketi (FIQ) ve Kadın Cinsel İşlev Ölçeği'nden (FSFI) oluşan 3 anket verildi.

Bulgular: Hastaların ortalama yaşı 40,3±8,5 yıl; ortalama VKİ 27,1±4,4 kg/m^2' idi; hastaların son bir haftalık VAS 6,9±2 cm; PSQI ortalaması 24,8±10,8 (PSQI≤5 olan 1 hasta), FIQ 65,9±19,2; FSFI 19,0±6,9 idi. PSQI ortalaması ile VKİ değerleri arasında anlamlı ilişki gözlenmedi (p=0,401); son 1 haftalık VAS, FIQ, FSFI ortalama değerleri arasında ise anlamlı ilişki gözlendi (p=0,03, p=0,034, p=0,000 sırası ile). Pearson korelasyon analizinde PSQI değerleri ile VAS değerleri (r=0,324; p=0,000) ve FIQ değerleri (r=0,271; p=0,001) pozitif korele olarak bulundu. FIQ değerleri ile son 1 haftalık VAS değerleri arasında anlamlı ilişki (p=0,000) saptandı. P<0,005 değeri istatistiksel olarak anlamlı kabul edildi.

Sonuç: Uyku bozukluğu FMS hastalığında pek çok semptom ve bulgunun temelinde yatan bozukluk olarak görülmektedir. FMS'li kadınlarda seksüel disfonksiyon hastalığın şiddetine, kötü uyku kalitesine bağlı gelişebilir. Çalışmamızda uyku disfonksiyonunun hastalık ciddiyeti, ağrı ve seksüel disfonksiyon ile belirgin ilişkili olarak bulduk. Ayrıca VAS ve PSQI arasında pozitif korelasyon bulduk.

Anahtar Kelimeler: Fibromiyalji sendromu, seksüel disfonksiyon, uyku bozukluğu

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Introduction

Fibromyalgia syndrome (FMS) is an entity with multiple concomitant disorders, rather than a single disorder. The common symptoms of FMS include sleep disorders, affective disorders, chronic generalized pain, and fatigue. The pathophysiology of FMS has yet to be elucidated, and no treatment is available for relieving all of the symptoms[1]. Several studies in the literature have found a close correlation between FMS and sexual dysfunction. The main symptoms include decreased sexual drive, excitement, orgasm, and increased genital pain[2]. From a psychological point of view, stress, chronic generalized pain, fatigue, and sleep disorder negatively affect the sexual life of patients with FMS. In addition, the medicines used for treating the disease are also known to negatively affect sexual function[2]. Sleep problems are one of the most common symptoms in patients with FMS[3]. This study reviews the relationship between disease progress, sleep problems, and sexual dysfunction.

Materials and Methods

A total of 140 sexually active, pre- or postmenopausal women who presented to our physical medicine and rehabilitation outpatient clinic between January 2016 and June 2016 who was diagnosed FMS in accordance with the American College of Rheumatology 1990[4] and 2010 criteria, were enrolled in the study. The exclusion criteria included pregnancy, breastfeeding, major depression, active infection or inflammation, and malignancies. The patients' age, height, body weight, body mass index (BMI), and general pain score for the last 1 week were recorded. The patients were given three different sets of questionnaires: the Pittsburgh Sleep Quality Index (PSQI), Fibromyalgia Impact Questionnaire (FIQ), and Female Sexual Function Index (FSFI) in order to evaluate sleep function, disease severity, and sexual function.

The FIQ was developed by Burckhardt to evaluate the functional status, disease progression, and outcomes of patients with fibromyalgia. The Turkish version of the FIQ was validited by Sarmer et al.[5]. The scale is used to follow up the conditions and outcomes of patients with FMS. The first item consists of 10 Likert-type questions. In the second and third items, the patient is asked to tick days to allow for the determination of "disease exposure" and "absence from work." The scores obtained are adapted to 10. The remaining seven questions are based on marking the corresponding points in the equivalent visual scale. The scoring interval is 0-100.

The PSQI scale provides information about the type and severity of sleep disorder and sleep quality in the last 1 month. Out of a total of 24 questions, 19 questions are answered by the patient, and the remaining 5 are answered by the partner of the patient. Using the 19 questions answered by the patient, 7 subdimensions are evaluated, including the subjective sleep quality, sleep latency, sleep duration, routine sleep activity, sleep disorder, use of sleeping pills, and daytime dysfunction. Each item in the scale is graded from 0 (no problem at all) to 3 (severe problem). The total scores for the seven subdimensions give the total PSQI score. A total score of 5 and less indicates that the sleep quality is "good"[6]. The Turkish validity of the scale was provided by Agargun et al.[7]. The FSFI was developed by Rosen et al.[8] in 2000 as a multidimensional scale consisting of 6 parts and 19 items to assess sexual function in women. Six dimensions are involved in the scale: desire, excitement, lubrication, orgasm, satisfaction, and pain. The lowest score on the scale is 2.0, and the highest is 36.0. The coefficient is 0.6 for the first and second questions; 0.4 for questions 3-10; and 0.3 for questions 11-19. The study was approved by the local Ethics Committee (2015-58) and was performed in accordance with the ethics standards described in an appropriate version of the 1975 Declaration of Helsinki.

Statistical Analysis

SPSS version 21 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.) was used for data analysis. The normal distribution of data was checked using the Kolmogorov-Smirnov test. A comparison was made for each parameter. The t test was used for normally distributed groups, and the Mann-Whitney U test was used for abnormal distribution. Chi-square analyses were used for a detailed examination of differences across groups. We used the one-way ANOVA test to compare continuous variables. Regression analyses were run for comparing multiple variables. Pearson's correlation analysis was used as the correlation analysis. The significance of these tests was defined as $p \leq 0.05$.

Results

A total of 140 sexually active women aged 17-67 years who were diagnosed as having FMS were enrolled in this study. The mean age of the patients was 40.3±8.5 years, the mean BMI was 27.1±4.4, the general pain score [visual analogue scale, (VAS)] in the last 1 week was 6.9±2 cm, the mean PSQI was 24.8±10.8 (one patient with PSQI ≤5), the mean FIQ was 65.9±19.2, and the mean FSFI was 19.0±6.9. The descriptive data of the study are summarized in Table 1. Based on the results of the Kolmogorov-Smirnov test, it was observed that the FIQ, FSFI, and PSQI data did not have a normal distribution ($p=0.032$; $p<0.001$; $p=0.002$, respectively) (Table 2). All parameters were compared with each other using regression analysis and the Mann-Whitney U test. No significant relationship was observed between the mean PSQI and BMI values ($p=0.401$), whereas a significant relationship was found between the mean VAS values (last 1 week), FIQ, and FSFI ($p=0.03$; $p=0.034$; $p<0.001$; respectively) (Table 3).

In the Pearson's correlation analysis, a positive correlation was found between the PSQI and VAS ($r=0.324$; $p=<0.001$; $p<0.001$) and FIQ values ($r=0.271$; $p=0.001$). No correlation was found between the PSQI and FSFI values ($p=0.645$). The FSFI values were compared with all other parameters using regression analysis and the Mann-Whitney U test. No

statistically significant relationship was observed between the FSFI, FIQ, and BMI values (p=0.183; p=0.682, respectively) (Table 3). A significant relationship was observed between the FSFI and PSQI values, age (in favor of younger ages) (p<0.001); no correlation was determined (r=0.27, p=0.325; r=0.57, p=0.251). A significant relationship was found between FIQ and VAS values (last 1 week) (p<0.001) (Table 3). A p value <0.005 was considered statistically significant.

Discussion

Many functions of sex hormones may affect chronic pain syndromes such as migraine, headaches, FMS, inflammatory arthritis and back ache, and others[8]. Scientific research has shown sex-specific differences in pain sensitivity and threshold. Although the underlying pathogenetic mechanism responsible for these differences has not yet been defined, the probability of a sex hormone effect on the nociceptive process has attracted attention[9].

The pathophysiology of FMS includes alterations in ascending and descending central nervous and peripheral nerve pathways, which lead to increased pain and sensitivity. Research on the risk factors has focused on several genetic predispositions and the effects of stress and poor sleep[10]. Recent human neuroimaging studies suggested that FMS, a chronic widespread pain disorder, exhibited altered thalamic (modulation of pain) structure and function[11]. The exact etiology of FMS is unknown, and the pathogenesis involves psychology, environmental, genetics, hormonal (serotonin), and impaired sleep quality. Brooks et al.[12] found that gynecologic, endocrine, and autoimmune diagnoses were associated with a diagnosis of FMS. They also found a relationship between the timing of gynecologic surgery and pain onset in FMS. Patients with FMS commonly have various autoimmune, endocrine, gynecologic, or psychiatric disorders. Sexual dysfunction related to chronic fatigue syndrome has become an increased concern rceently; however, limited studies have analyzed this subject to date. FMS may cause sexual dysfunction as a result of impaired emotional state. Whether the partners of female patients with FMS also have impaired sexual life has been the subject of various investigations[13]. Blazquez et al.[14] analyzed the sexual function of 615 patients with chronic fatigue syndrome, and remarked that frequency of sexual dysfunction with FMS, Sjögren syndrome, and Myofacial pain syndrome concerned cognitive, neurologic, and neurovegetative symptoms were higher.

Chronic generalized pain is the cardinal symptom of FMS, and results in decreased quality of life, along with physical and psychosocial impairments. Burri et al.[15]. reported difficulty in lubrication, sexual pain, and increased sexual stress in female patients with FMS who presented with chronic generalized pain. Terzi et al.[16] determined a lower threshold of pain and a higher number of tender points in women with FMS who presented with dyspareunia compared with those without

Table 1. Descriptive data

		Age	BMI	PSQI	FIQ	FSFI	VAS
n	Valid	140	140	140	140	140	140
Mean		40.34	27.19	24.89	65.97	19.08	6.94
Median		40.00	27.30	23.00	67.50	20.50	7.00
Standard deviation		8.57	4.42	10.81	19.22	6.98	2.00

BMI: Body mass index, FIQ: Fibromyalgia Impact Questionnaire, FSFI: Female Sexual Function Index, PSQI: Pittsburgh Sleep Quality Index, VAS: Visual analog scale

Table 2. Tests of normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Significance	Statistic	df	Significance
FSFI	0.12	140	0.000	0.95	140	0.000
PSQI	0.10	140	0.002	0.97	140	0.008
FIQ	0.79	140	0.032	0.97	140	0.004

[a]Lilliefors significance correction. FIQ: Fibromyalgia Impact Questionnaire, FSFI: Female Sexual Function Index, PSQI: Pittsburgh Sleep Quality Index

Table 3. Multiple Comparisons of the parameters

p value	BMI	FIQ	PSQI	VAS	FSFI
FSFI	0.183	0.682	<0.001	-	-
PSQI	0.401	0.034	-	0.03	<0.001

BMI: Body mass index, VAS: Visuel analog scale, FIQ: Fibromyalgia Impact Questionnaire; FSFI: Female Sexual Function Index, PSQI: Pittsburgh Sleep Quality Index

dyspareunia. The central pathophysiology in the development of dyspareunia in female patients with FMS still needs further investigation. Ghizzani et al.'s[17] results supported that coital pain develops with the severity of FMS symptoms depending on the cooperative effect of peripheral and central sensitization mechanisms in female patients with FMS.

Palagini et al.[1] hypothesized that sleep disorders activate stress and inflammation systems, playing a central role in all other symptoms. This also accounts for the high frequency of togetherness with pain, sleep, and mental disorders. Starting from this point of view, it is suggested that the treatment of sleep disorders may help alleviate symptoms of FMS and mental disorders. In a study similar to the present study, which was performed by Amasyali et al.[18] in 54 patients, a positive correlation was observed between the patients with PSQI score >5 (poor sleep quality) and sexual dysfunction. Additionally, a marked link was found between the high FIQ scores and sexual dysfunction. The present study found poor sleep quality to be markedly associated with the pain score, severity of disease, and sexual dysfunction. No marked link was found between BMI and sleep disorder and sexual dysfunction. The rates of sexual dysfunction and poor sleep quality are higher at older ages. Hence, it is concluded that reductions in generalized pain, severity of disease, and sleep disorder may also reduce sexual problems in patients. In FMS, multiple symptoms are closely associated with each other, and sleep disorder appears to play a main function in the development of all other symptoms. FMS is a chronic pain syndrome characterized by subjective primary insomnia. It shows abnormalities in the continuity and architecture of sleep in polysomnographic findings. Reduced quality of sleep, increased awakening, reduced slow-wave sleep, and emergence of abnormal alpha waves (alpha-delta) in nonrapid eye movement sleep are seen in sleep recordings[19]. FMS symptoms are considered to be related to nonrestorative sleep disorder associated with alpha-electroencephalogram sleep disorders. Additionally, patients with FMS may also report sleep disorders such as sleep apnea or periodic limb movements[19,20]. Diaz-Piedra et al.[3] observed a lower sleep quality, a greater wake phase, and a higher number of awakenings in a one-night polysomnographic evaluation of patients with FMS compared with a control group. It was also seen that patients reported poor subjective sleep quality[3]. Stuifbergen et al.[20] evaluated the sleep disorders of 104 female patients with FMS and reported subjective sleep disorder in 44% of the patients and objective sleep disorder in 21%. In patients with objective sleep disorders, the pain score, tender point index, and FIQ scores were higher, and also more depressive symptoms were observed compared with the others.

Miro et al.[21] studied whether patients with FMS had different cognitive alterations depending on their sex. According to the study, treatments aimed at decreasing emotional distress seemed to improve attention more in women than in men; those intended to improve sleep quality were likely to reduce alertness incompetency in women and executive problems in men. Similar to the literature, we found a statistically significant association with sleep disfunction, disease severity, pain, and sexual disfunction. In contrast to the literature, we found a positive correlation between sleep disfunction, disease severity, and pain. It has been estimated that pain is positively correlated with disease severity and poor sleep quality. According toour findings, BMI has no effect on sleep, disease severity, pain and sexual function. Our patient population was overweight and middle-aged to fit with FMS. We also found fewer sexual disfunction symptoms at younger ages.

The treatment of FMS involves pharmacologic (tricyclic antidepressants, antiepileptic agents, selective serotonin uptake inhibitors) and nonpharmacologic (massage, exercise, acupuncture) therapies[10]. No drug is recuperative for all of the symptoms of FMS. When scheduling the treatment plan, it is necessary to take into consideration that FMS consists of multiple closely-associated symptoms[10]. Therefore, behavioral programs should be included to increase (deep sleep) and improve poor sleep quality, which is the most common symptom. Therapeutic measures should be taken, the adverse effects of drugs should be minimized, and a multidisciplinary approach should be used to improve the patient's quality of life.

Study Limitations

First, our patients' age range was very wide (17 years up to 67 years old). Age has a major affect on both sleep quality and sexual life. The study includes both pre- and post-menopausal women. The status of menopause is another confounding factor that is in itself a cause for worse sexual domain scores compared with premenopausal women. In addition, related to menopause, some other sexual function questionnaires were developed for menopausal women. We did not consider the menopausal status of our patients with any questionnaire or laboratory examinations. Additionally, medication may have affected our study results; we did not ask about medicine use for menapause or FMS. The study is a single-centered study and our clinic is located at one of the eastern cities in Turkey. Literate patients filled out scales by themselves, but most illiterate patients did not want to complete the FSFI scale; therefore, we had to exclude them. It would be have been better if we had asked about the patients' educational levels.

Conclusion

Sleep disorder is regarded as the underlying cause for many signs and symptoms in FMS. Sexual dysfunction may develop in women with FMS due to the potency of the disease and poor sleep quality. We found that sleep dysfunction was significantly related with the severity of disease, pain and sexual disfunction. We also found a positive correlation between VAS and PSQI (when pain scor is higher, sleep disorder is seen more prevelant). Therefore, beyond others, the treatment of sleep disorder is of vital importance in the management of FMS.

Ethics

Ethics Committee Approval: The study were approved by the İnönü University of Local Ethics Committee. Informed Consent: Consent form was filled out by all participants.
Peer-review: Externally and Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Tuba Tülay Koca, Günseli Karaca Acet, Concept: Tuba Tülay Koca, Design: Tuba Tülay Koca, Data Collection or Processing: Tuba Tülay Koca, Günseli Karaca Acet, Analysis or Interpretation: Tuba Tülay Koca, Literature Search: Tuba Tülay Koca, Emrullah Tanrıkut, Burcu Talu, Writing: Tuba Tülay Koca.
Conflict of Interest: No conflict of interest was declared by the authors.
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References

1. Palagini L, Carmassi C, Conversano C, Gesi C, Bazzichi L, Giacomelli C, et al. Transdiagnostic factors across fibromyalgia and mental disorders: sleep disturbances may play a key role. A clinical review. Clin Exp Rheumatol 2016;34:S140-4.
2. Bazzichi L, Giacomelli C, Rossi A, Sernissi F, Scarpellini P, Consensi A, et al. Fibromyalgia and sexual problems. Reumatismo 2012;64:261-7.
3. Diaz-Piedra C, Catena A, Sanchez AI, Miro E, Martinez MP, Buela-Casal G. Sleep disturbances in fibromyalgia syndrome: the role of clinical and polysomnographic variables explaining poor sleep quality in patients. Sleep Med 2015;16:917-25.
4. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33:160-72.
5. Sarmer S, Ergin S, Yavuzer G. The validity and reliability of the Turkish version of the Fibromyalgia Impact Questionnaire. Rheumatol Int 2000;20:9-12.
6. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193-213.
7. Agargun MY, Kara H, Anlar O. Pittsburg uyku kalitesi indeksinin geçerliliği ve güvenilirliği. . Turk Psikiatri Dergisi 1996;7:107-15.
8. Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther 2000;26:191-208.
9. Maurer AJ, Lissounov A, Knezevic I, Candido KD, Knezevic NN. Pain and sex hormones: a review of current understanding. Pain Manag 2016;6:285-96.
10. Chinn S, Caldwell W, Gritsenko K. Fibromyalgia Pathogenesis and Treatment Options Update. Curr Pain Headache Rep 2016;20:25.
11. Lim M, Kim JS, Kim DJ, Chung CK. Increased Low- and High-Frequency Oscillatory Activity in the Prefrontal Cortex of Fibromyalgia Patients. Front Hum Neurosci 2016;10:111.
12. Brooks L, Hadi J, Amber KT, Weiner M, La Riche CL, Ference T. Assessing the prevalence of autoimmune, endocrine, gynecologic, and psychiatric comorbidities in an ethnically diverse cohort of female fibromyalgia patients: does the time from hysterectomy provide a clue? J Pain Res 2015;8:561-9.
13. Yener M, Askin A, Soyupek F, Akpinar A, Demirdas A, Sonmez S, et al. The evaluation of anxiety and depression status in spouses of sexually active reproductive women with fibromyalgia. Clin Exp Rheumatol 2015;33:S20-4.
14. Blazquez A, Ruiz E, Aliste L, Garcia-Quintana A, Alegre J. The effect of fatigue and fibromyalgia on sexual dysfunction in women with chronic fatigue syndrome. J Sex Marital Ther 2015;41:1-10.
15. Burri A, Lachance G, Williams FM. Prevalence and risk factors of sexual problems and sexual distress in a sample of women suffering from chronic widespread pain. J Sex Med 2014;11:2772-84.
16. Terzi H, Terzi R, Kale A. The relationship between fibromyalgia and pressure pain threshold in patients with dyspareunia. Pain Res Manag 2015;20:137-40.
17. Ghizzani A, Di Sabatino V, Suman AL, Biasi G, Santarcangelo EL, Carli G. Pain Symptoms in Fibromyalgia Patients with and without Provoked Vulvodynia. Pain Res Treat 2014;2014:457618.
18. Amasyali AS, Tastaban E, Amasyali SY, Turan Y, Kazan E, Sari E, et al. Effects of low sleep quality on sexual function, in women with fibromyalgia. Int J Impot Res 2016;28:46-9.
19. Dauvilliers Y, Touchon J. [Sleep in fibromyalgia: review of clinical and polysomnographic data]. Neurophysiol Clin 2001;31:18-33.
20. Stuifbergen AK, Phillips L, Carter P, Morrison J, Todd A. Subjective and objective sleep difficulties in women with fibromyalgia syndrome. J Am Acad Nurse Pract 2010;22:548-56.
21. Miro E, Martinez MP, Sanchez AI, Prados G, Lupianez J. Men and women with fibromyalgia: Relation between attentional function and clinical symptoms. Br J Health Psychol 2015;20:632-47.

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Evaluation of the efficacy of transobturator tape surgery in the treatment of stress urinary incontinence using urodynamics and questionnaires

Stres üriner inkontinas tedavisinde transobturator teyp operasyonunun etkinliğinin ürodinami ve anket formlarıyla değerlendirilmesi

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Abstract

Objective: To measure the efficiency of transobturator tape (TOT) surgery using urodynamics and questionnaires in stress urinary incontinence.
Materials and Methods: Ninety-two patients with stress and mixed urinary incontinency who underwent TOT surgery were selected for the study. We retrospectively examined the patients' urodynamics, ultrasonography, demographic characteristics, incontinency surveys, life quality scores [incontinence impact questionnaire, (IQ-7) and urinary distress inventory (UDI-6)], diagnostic findings, Q-type test, surgical records, and complications. Patients treatment adherence, life quality scores, and urodynamics were evaluated as per the findings and complications following discharge of the patients between 12 and 36 months. Patients with a surgical history as the result of incontinence were excluded from the study.
Results: Prior to surgery, 57 (61%, 95) patients had stress urinary incontinence (SUI), and 35 (38%, 05) patients had mixed urinary incontinence (MUI). During surgery, 45 (48%, 91) patients underwent extra pelvic surgical intervention. The mean follow-up time was 22.17±7.55 months. Our subjective success rate was 91%, 3 and the objective success rate was 78%, 3. In the life quality evaluation, a statistically significant improvement was found between IIQ-7 and UDI-6 scores. Parity over 4 was an important failure reason. Two (2%, 17) patients developed vaginal erosion, 2 (2%, 17) of the patients developed temporary urine retention, and 1 (1%, 08) patient developed nova urge incontinence.
Conclusion: Our study demonstrates that TOT surgery provides high objective and subjective success and has a positive impact on life quality. The ease of application and lower complication rate makes TOT a valuable alternative for other treatment approaches in the surgical treatment of SUI.
Keywords: Stress urinary incontinence, Q-type test, transobturator tape surgery, urodynamic

Öz

Amaç: Stres üriner inkontinans (SÜİ) tedavisinde, transobturator teyp (TOT) operasyonunun etkinliğinin, ürodinami ve anket formları ile değerlendirilmesi.
Gereç ve Yöntemler: Stres ve miks üriner inkontinans (MÜİ) tanısı ile TOT uygulanan 92 hasta çalışmaya dahil edildi. Hastaların demografik özellikleri, inkontinans anketleri, yaşam kalite skorları [incontinence impact questionnaire (IIQ-7) ve ürinary distres inventory (UDI-6)], muayene bulguları, Q tip test, ultrasonografi, ürodinami, operasyon ve komplikasyonları retrospektif olarak incelendi. Hastalar taburcu olduktan 12 ile 36 (22,17±7,55) ay sonra hasta şikayetleri, yaşam kalite skorları, ürodinami bulguları ve komplikasyonlar açısından değerlendirildi. Daha önce inkontinans nedeniyle opere olan hastalar çalışma dışı bırakıldı.
Bulgular: Ameliyat öncesi 57 hastada (%61,95) SÜİ, 35 hastada (%38,05) MÜİ mevcuttu. Operasyon sırasında 45 (%48,91) hastaya ilave pelvik cerrahi müdahale uygulandı. Subjektif başarı oranımız %91,3, objektif başarı oranımız %78,3'tü. Yaşam kalitesi değerlendirilmesinde IIQ-7 ve UDI-6 skorlarında istatistiksel olarak anlamlı düzelme saptandı. Paritenin 4'ün üzerinde olması önemli bir başarısızlık nedeni idi. İki (%2,17) hastada vajinal erezyon, 2 (%2,17) hastada geçici idrar retansiyonu, 1 (%1,08) hastada ise de nova urge inkontinans gelişti.
Sonuç: Çalışmamız TOT operasyonunun yüksek objektif ve subjektif başarı sağladığını, yaşam kalitesinin iyi yönde etkilediğini göstermiştir. Uygulama kolaylığı ve komplikasyon oranının düşük olması sebebiyle SÜİ'nin cerrahi tedavisinde diğer tedavi yaklaşımlarına değerli bir alternatiftir.
Anahtar Kelimeler: Stres üriner inkontinans, Q tip test, transobturator teyp ameliyatı, ürodinami

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Introduction

The International Continence Association (ICS) described Urinary Incontinence (UI) as unintended urine continence that becomes a social and hygienic problem[1]. Two hundred fifty million adult individuals are effected by UI around the world, between 7-37% of women aged between 20-39 years experience UI[2,3]. In Turkey, it is known that the prevalence of UI in women ranges between 16.4% and 49.7%[4]. Incontinence is a serious issue that results in loneliness, economic problems, and has a negative effect on an individual's sexual life by causing shame, declining confidence, and a decrease in social activities[5]. Although there are many risk factors that result in incontinence, the most apparent risk factors in women are old age and trauma experienced during delivery through pregnancy and higher parity numbers, and births with interventions and tears[6-9].

The most common type of incontinence experienced in women is stress urinary incontinence (SUI), which is seen commonly in middle aged and parous women, and experienced as a result of situations that increase the pressure on the abdomen such as coughing, laughing, and heavy lifting. Stress incontinence was described by the ICS as UI that occurs as a result of intravesical pressure overrunning urethra pressure without any increase in detrusor activity. Stress incontinence as an incontinence type, is the variety that patients can benefit the most from surgery among the treatment options. Although there are different techniques available in treatment, there is no agreement as to which surgical intervention is the most efficient and appropriate for which patient. We use the classic external to internal transobturator tape (TOT) technique for patients who present to our clinic with SUI or mixed urinary incontinence (MUI). In this study we aimed to compare the subjective and objective success of TOT surgery with other surgical techniques, to demonstrate the short- and long-term complications, and its effects on patients' quality of life in light of the literature.

Materials and Methods

Our study comprised 125 patients with MUI and SUI who were treated with TOT surgery between April 2010 and April 2012 in İstanbul Training and Research Hospital, Gynecology and Obstetrics clinic. In line with data integrity and patient compliance, 92 of the patients were included in our study. The study was conducted in İstanbul Training and Research Hospital, Perinatology and Delivery Unit, following receipt of approval from the Hospital Training and Planning Committee and Committee of Ethics. Within the indicated dates, patients considered within the scope of the study were informed and included in the study after receiving their signed form of approval. Patients who had urge incontinence, undergone surgery for incontinence, had a significant neurologic disorder, had undergone previous vaginal surgery, or used medication that created a tendency to bleed were excluded from the study. We retrospectively examined the patients urodynamics, ultrasonography, demographic characteristics, incontinence surveys, life quality scores [incontinence impact questionnaire, (IQ-7) and urinary distress inventory (UDI-6)], diagnostic findings, Q-type test, surgical records, and complications. Also, we reviewed the patients' treatment adherence, life quality scores, urodynamics as evaluated per findings and complications following the discharge of the patients between 12 and 36 months. In the pre-operative period, the histories of the patients were collected and pelvic inspections, urinalysis, [(life quality tests: UDI-6 and incontinence impact questionnaire-7 (IIQ-7)], Q-type tests, urodynamics, and residual urine tests were conducted. The Baden-Walker classification was used to classify pelvic limb prolapsus in the pelvic inspection. Cough stress tests were positive for all the patients in our study. Cervix vesicae mobility was evaluated with Q-type test. If there was no reproduction in the urine culture taken prior to urodynamic testing, patients were proceeded to surgery; if reproduction was observed, patients were re-evaluated following appropriate antibiotic treatment. For conducting multi-channel cystometry, 8 F micro-type transducers (2 transducers positioned on the tip and 6 cm behind, positioned in a 3 o'clock direction) were placed transurethrally in the patient. Pressure measurements were conducted by connecting the system to the patient who was laid on the patient examination couch as they drained their urine, and examined for residual urine. The bladder was filled with sterile physiologic serum at 50 cc/minute at room temperature. During the filling procedure, the time to first sensation of urine, and first urge to urinate, normal urge to urinate, strong urge to urinate, and maximal bladder capacity (maximum pressure level of the patient before urinary incontinence) were evaluated. During measurements following the 200 cc physiologic serum, UI was induced using the Valsalva maneuver in the lithotomy position. It was re-applied as 100 cc if no continence was observed. Valsalva leak point pressure values (VLPP) were considered for defining SUI sub types. Intrinsic sphincter insufficiency was diagnosed for the patients with VLPP below or equal to 60 cm H_2O, and type 2 SUI was diagnosed for the patients with VLPP above or equal to 90 cm H_2O. Detrusor dysfunction was diagnosed using urodynamics through an immediate increase in basal detrusor pressure as 15 cm H_2O or more during the filling procedure.

For the decision of surgery, patient symptoms and urodynamic parameters were considered together. TOT procedures were conducted as external to internal as described by Delorme. All operations were performed using outside-in Obtryx (Boston Scientific, Natick, MA, USA) brand kits. All patients were administered intravenous 2 gr cefazolin sodium prior to surgery. A longitudinal incision of about 2 cm was made starting 0.5 cm from under the urethral meatus to the front wall of the vagina. Periurethral dissection was performed with blunt and sharp dissection until below the ischiopubic ramus. A bilateral 5-mm incision was made at the clitoris level, the lateral side of the labium majus, 15 mm lateral of the ischiopubic ramus. A hook-shaped

TOT needle was advanced medially by palpating the posterior of the ischiopubic ramus and m. obturatorius internus with an index finger, which was on the paraurethral dissection point, and passed through the dermis, obturator membrane, and incision in the vagina, respectively. After this procedure, we checked whether vaginal fornix and urethra perforation had occurred. The mesh-attached needle was removed from the dermis from the reverse side. The same method was applied to the other side. The strain of the mesh was adjusted to leave an opening to allow for a scissor tip to enter between the urethra and band at the end of the procedure. At the end of the procedure, an 18 F foley catheter was placed. The duration of TOT and other additional surgical procedures (if applicable) was recorded.

Additional pelvic floor interventions were performed on patients according to the indications. The patients' catheter were removed on postoperative day 1 and we waited for spontaneous urination. As a result of the evaluations, 57 patients with SUI and 35 patients with MUI were included in the study.

Statistical Analysis

SPSS version 11.0 was used for the statistical analysis of this study (Statistical Package for the Social Sciences Inc; Chicago, IL, USA). Student's t-test, the Mann-Whitney U, paired t-test, Wilcoxon rank test, Fisher's exact test, and chi-square tests were used for comparisons. $P<0.05$ were accepted as statistically significant.

Results

A total of patients 125 underwent TOT. In line with data integrity and patient compliance, 92 patients were included in our study. The average of the patients was 48.46 years (range, 29- 83 years). Fifty patients were premenopausal and 42 were postmenopausal patients. None of the postmenopausal patients were receiving hormone replacement treatment. The average menopause duration for patients who were postmenopausal was 10.12 years (range, 1-40 years). The mean follow-up duration was 22.17 months (range, 12-36 months). The average parity was 3.42 (range, 1-15); 4 patients had a history of cesarean section, and 2 patients had a history of vacuum-assisted birth. The average baby birth weight was 3708.26 gram (range, 2600-6000 g). The average duration of incontinence was 6.83 years (range, 1-40 years). The average body mass index (BMI) was calculated as 28.51± 4.3 kg/m^2 (range, 23.3-39.5 kg/m^2). According to BMI, 58.69% of the patients were overweight and 33.69% were obese. No patients were morbidly obese. Forty-one patients had systematic diseases: hypertension (n=16), diabetes (n=8), thyroid disease (n=5), chronic obstructive pulmonary disease (COPD) (n=6), hypertension + diabetes (n=4), and hypertension + COPD (n=2). Twenty (21.73%) patients had undergone previous gynecologic operations, none of which were in relation with incontinence; 6 (6%, 52) operations were hysterectomy. Thirty-five patients (38.05%) were diagnosed as having MUI and 57 patients (61.95%) were diagnosed as having SUI as a result of anamnesis, examinations, and urodynamic inspections. Patients with pure urge incontinence were excluded. All patients had symptoms of stress incontinence and cough stress test results were positive. Table 1 shows the demographic and clinical characteristics of the patients (Table 1).

All patients underwent external to internal TOT procedures. Forty-five (48.91%) patients underwent additional procedures as per indication during the same surgical period: vaginal hysterectomy + anterior colporrhaphy (VAH + CAP) (n=5), anterior colporrhaphy (n=3), posterior colporrhaphy (n=23), manchester (n=3), anterior posterior colporrhaphy (n=4), abdominal hysterectomy + bilateral salpingo-ophorectomy (total abdominal hysterectomy + buthionine sulfoximine) (n=4), bilateral tube ligation, cyst extirpation (n=1).

No intraoperative complications developed in the patients in the present study. No hematomas, wound site infections, or urinary system infections developed during the postoperative stage. Two (2.17%) patients developed a foreign body reaction. However, no interventions were conducted on the patients because the erosion in the vagina was less than 1 cm and asymptomatic. The patients were taken to follow-up. One (1.08%) patient developed incontinence and this patient was treated with anticholinergic agents.

Table 1. Demographic and clinical characteristics of the patients

Parameter	The number of patients who underwent TOT (n=91)
Age (range) years	48.46±10.37 (29-83)
BMI (range) kg/m^2	28.51±4.35 (23.3-39.5)
Parity	3.41±1.84 (1-15)
Baby birth weight (kg)	3708.26±508.04 (2600-6000)
Duration of symptoms (years)	6.83±6.428 (1-40)
Follow-up duration (months)	22.17±7.55
Systematic diseases n (%)	
Hypertension	16 (17)
Diabetes	8 (8.5)
Thyroid disease	5 (5.4)
COPD	6 (6.5)
Hypertension + diabetes	4 (4.3)
Hypertension + COPD	2 (2.1)
Menopause, n (%)	42 (45.6)
Incontinence types of the patients n (%)	
Pure stress incontinence	57 (61.95)
Mixed incontinence	35 (38.05)

BMI: Body mass index, SD: Standard deviation, COPD: Chronic obstructive pulmonary disease, TOT: Transobturator tape

The 35 patients with MUI were started on trospium chloride one week prior to operation and treatment continued following the operation. Patients were re-evaluated after an average of 22.17 months (range, 12-36 months). Patients were primarily evaluated at follow-up examinations as per their symptoms. Examinations, urodynamics, Q-type test, UDI-6, and IIQ surveys were conducted: one patient (1.1%) had worsened symptoms and 12 (13%) patients' symptoms were improved, no significant changes were observed in 7 (7.6%) patients, and 72 (78.3%) were symptom free. The results were compared with the results obtained at the preoperative stage.

The first two questions of the UDI-6 survey are regarding symptoms of irritation and the 4th question is about stress symptoms, the 5th and 6th questions are related with obstruction; these questions are evaluated by grouping them individually. An average 1.02 score decrease was seen in the pre- and post-operative UDI-6 evaluations for the 1st and 2nd questions, an average 3.66 score decrease was seen for the 4th question, and a 4.57 score decrease was found for the 5th and 6th questions. All questions in UDI-6 and IIQ-7 saw an average score decrease of 10.86. The decrease in each evaluation was found statistically significant, which proved the positive effect on life quality ($p<0.01$). The 5th and 6th questions of UDI-6 had no statistically significant change ($p>0.05$) (Table 2).

Seventy-two the patients (78.3%) were identified as having objective cure when the post-operative urodynamics were evaluated. Stress incontinence remained in 20 (21.7%) patients. Objective success was obtained in 65 out of 81 (80.2%) patients with anatomic incontinence, and 7 out of 11 (63.6%) patients with type 3 incontinence. There were no statistically significant differences between TOT success and stress anticontinence subtypes.

Regarding the patients with successful and unsuccessful operations, it was found that parity over 4 was an important reason for failure. Age, BMI, heavy baby birth weight, and duration of symptoms had no significance over the success of the operation (Table 3).

Table 2. Evaluation of urinary distress inventory-6 and incontinence impact questionnaire-7 scores of the patients

	Preoperative	Postoperative	p
IIQ-7	13.13±3.70	2.27±4.41	<0.001***
UDI-6	6.49±2.50	1.92±2.53	<0.001***
UDI-6 1. 2. question	1.71±1.49	0.70±1.17	<0.001***
UDI-6 3. 4. question	4.27± 0.93	0.61±1.23	<0.001***
UDI-6 5. 6. question	0.5326±0.9193	0.5435±0.8946	0.876

***p<0.01: Statistically significant, SD: Standard deviation, IIQ: Incontinence impact questionnaire-7, UDI: Urinary distress inventory

Forty-five (48.91%) patients underwent additional operations as per the indication during the same operative period. There was no significant difference regarding TOT success between patients with without additional pelvic surgical operations. Six (6.5%) patients had a history of hysterectomy; no statistically significant difference was observed between patients with and without a history of hysterectomy.

There was no statistically significant difference in the time to first sensation of urine and maximum bladder capacity regarding the pre-operative and post-operative cystometry values. There was a significant decline in the frequency of daytime and nighttime micturition among the patients ($p<0.01$). There were no significant difference between the residual urine quantity after an average of 22.17 months for the pre- and post-operative periods ($p>0.05$). According to the Q-type test results, there was no significant change in the mobility of the cervix vesicae ($p>0.05$) (Table 4).

Table 3. Effects of various parameters on objective success

Post-operative urodynamics	Normal (mean ± SD)	SUI (mean ± SD)	p
Follow-up duration (months)	22.56±7.43	20.80±8.02	0.361
Age	46.88±9.40	54.15±11.88	0.005
BMI	28.62±4.73	28.13±2.60	0.659
Parity	3.15±1.08	4.40±3.25	0.007**
Heavy baby birth weight	3699.44±519.32	3740.00±476.65	0.754
Duration of symptoms	6.42±5.20	8.30±9.67	0.248

p<0.05, BMI: Body mass index, SUI: Stress urinary incontinence, SD: Standard deviation

Table 4. Changes in cystometry values

	Preoperative (mean ± SD)	Postoperative (mean ± SD)	p
First urine urge	147.39±27.94	143.69±31.95	0.421
Maximum capacity	427.60±69.31	410.86±60.24	0.062
Residual urine	12.010±9.89	14.34±9.52	0.102
Q angle	45.37±12.85	45.18 ±12.63	0.293
Number of urinations in daytime	7.42±1.798	5.34±1.354	0.001**
Number of urinations in nighttime	1.34±0.702	0.98±0.502	0.001**

p<0.05, SD: Standard deviation

Discussion

The TOT procedure is commonly used in the treatment of UI. One of the most important characteristics that distinguishes TOT procedures from other sling operations is the low rate of complications. The most important complications of the burch procedure are difficulties with urination and an increase in prolapsus after the operation[10]. For transvaginal tape procedures, complications include major limb injuries, bladder perforation, and bleeding[11]. Although the low rate of complications were remarkable when the results of the TOT procedures were first published, an increase in general complication rates and different complications indigenous to TOT were reported as the follow-up durations and number of cases increased. Along with the possibility of experiencing extensive bleeding, wound site infections, obturatory abscess, urinary retention, and re-operation related with mesh erosion, leg and groin pains were also reported for TOT operations[12]. Madjar et al.[13] suggested considering abdomen and pelvis tomography for patients with abdomen pain or urinary symptoms following sling procedures. The risk of vaginal erosion is between 0% and 2.7% following the TOT procedures[14]. The most important complication observed in our study was vaginal erosion (n=2, 2.17%).

Post-operative urinary retention can be connected to edema or pain but dysuria or urine retention that continues after one week must be considered seriously. If necessary, the tape must be loosened with traction and re-inserted properly using the same vaginal incision[15]. In another study, bladder exit obstruction was identified in 3.8% of participants following TOT, and it was stated that removal or loosening of the tape as early as possible could be beneficial in the presence of a clinically significant obstruction[16]. In our study 2 patients (2.17%) had temporary urine retention following the operation. For these patients catheters were left in the bladder for 1 week. Patients urinated comfortably after the removal of the catheters and no additional operations were required because the residual urine quantity was below 100 mL. One patient (1.08%) had novo urge incontinence in the post-operative period; this rate was 2% in the study conducted by Juma and Brito[17].

For sling operations, it is not necessary to fix the urethral mobility. On the contrary, continuation of urethral mobility in the post-operative period provides dynamic bending for the urethra during stress[18]. In our study, urethral mobility was observed as continuous in the Q-type test, and there were statistically significant changes in the pre- and post-operative values.

In our study, UDI-6 and IIQ-7 forms, which were developed by Uebersax, were used to evaluate life quality before and after the TOT procedures. These forms have been used to evaluate life quality in most studies related with TOT[17,19]. The patients' survey answers were grouped, scored, and the pre- and post-operative scores were compared. When the UDI-6 stress (3rd and 4th questions) and urge (1st and 2nd questions) values were evaluated, the scores were found significantly decreased. No changes were noted in the obstructive (5th and 6th questions) scores. Similar results were reported in the studies conducted by Juma and Brito[17] and Grise et al.[20]. The decline of both stress and urge symptoms reminded us of the integral theory of Petros and Ulmsten[21]. Our data are in accordance with this theory.

There was a statistically significant increase in patients' life quality scores in the post-operative period in IIQ-7 scores, which shows that the operations were successful. During the follow-up evaluations as per the symptoms, 12 (13.04%) patients reported a decline in incontinence symptoms, and 72 (78.03%) patients were considered cured. According to this result, 91.3% of patients achieved subjective success and this result is in accordance with the literature. Subjective success rates range between 78% and 91% in the literature[19,20]. Seven patients (7.06%) reported no significant change and 1 (1.08%) patient described worsened symptoms and with urge incontinence being added to their stress incontinence. According to the general urodynamic results, 72 (78.3%) patients obtained objective cure. Objective success rates in the literature range between 75% and 89.3%[20,22].

The number of pregnancies and parity, UI level, unsuccessful surgical operations in the past, VLPP ≤60 cm H_20, and BMI <30 the operation observed in the study conducted by Rodriguez et al.[23] as not effecting the unwanted side effects and surgical success. In the same study, the effects of the urodynamic measures on SUI surgical treatment cure rates and VLPP were found not to affect the surgical treatment result. In our study, no significant effect for age, duration of symptoms, type of incontinence, heavy baby birth weight and BMI was found to affect treatment success. Parity over 4 was identified as a significant reason for failure.

TOT is commonly conducted with other interventions. In a study that investigated whether the effects of the procedures on the pelvic floor affected TOT success rates, only 2 patient groups were compared; those who underwent TOT procedures, and patients with additional operations[24]. In that study, the authors found that additional pelvic interventions had no effect on TOT success. Forty-five patients (50.6%) underwent additional pelvic operations besides TOT. No significant difference was found between patients with and without additional operations in terms of TOT operation success.

Conclusion

Stress incontinence continues to be an important health issue. TOT is a method that is easy to apply with low complication rates and a high rate of success. Our results show the high success rate and low complication rate of TOT procedures. In our study, TOT was considered an efficient and reliable method in accordance with the success rates obtained. However, there is a need for further random prospective studies with different

methods and large populations in which long-term results are reported and compared.

Ethic

Ethics Committee Approval: Ethics committee approval was received for this study from the Institutional Review Board, Informed Consent: Written informed consent was obtained from patients who participated in this study.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Cihan Aygül, Ramazan Özyurt, Concept: Serkan Kumbasar, Design: Bulay Aytek Şık, Data Collection or Processing: Cihan Aygül, Analysis or Interpretation: Serkan Kumbasar, Literature Search: Ramazan Özyurt, Writing: Bulat Aytek Şık.
Conflict of Interest: No conflict of interest was declared by the authors.
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References

1. Abrams P, Andersson KE, Birder L, Brubaker L, Cardozo L, Chapple C, et al. Fourth International Consultation on Incontinence Recommendations of the International Scientific Committee: Evaluation and treatment of urinary incontinence, pelvic organ prolapse, and fecal incontinence. Neurourol Urodyn 2010;29:213-40.
2. Beji NK, Ozbas A, Aslan E, Bilgic D, Erkan HA. Overview of the social impact of urinary incontinence with a focus on Turkish women. Urol Nurs 2010;30:327-34.
3. Buckley BS, Lapitan MC, Epidemiology Committee of the Fourth International Consultation on Incontinence P. Prevalence of urinary incontinence in men, women, and children--current evidence: findings of the Fourth International Consultation on Incontinence. Urology 2010;76:265-70.
4. Basak T, Kok G, Guvenc G. Prevalence, risk factors and quality of life in Turkish women with urinary incontinence: a synthesis of the literature. Int Nurs Rev 2013;60:448-60.
5. Bilgili N, Akın B, Ege E, Ayaz S. Kadınlarda üriner inkontinans sıklığı ve etkileyen risk faktörleri. . Türkiye Klinikleri J Med Sci 2008;28:487-93.
6. Onur R, Deveci SE, Rahman S, Sevindik F, Acik Y. Prevalence and risk factors of female urinary incontinence in eastern Turkey. Int J Urol 2009;16:566-9.
7. Zhu L, Li L, Lang J, Xu T, Wong F. Epidemiology of mixed urinary incontinence in China. Int J Gynaecol Obstet 2010;109:55-8.
8. Işıklı B, Yenilmez A, Kalyoncu C. Eskişehir Alpu ilçesi 18 yaş üstü kadınlarda üriner inkontinans, risk faktörleri ve yaşam kalitesine etkisi: bir toplum tabanlı çalışma. Nobel Med 2011;7:34-9.
9. Kirss F, Lang K, Toompere K, Veerus P. Prevalence and risk factors of urinary incontinence among Estonian postmenopausal women. Springerplus 2013;2:524.
10. Kjolhede P. Long-term efficacy of Burch colposuspension: a 14-year follow-up study. Acta Obstet Gynecol Scand 2005;84:767-72.
11. Latthe PM, Foon R, Toozs-Hobson P. Transobturator and retropubic tape procedures in stress urinary incontinence: a systematic review and meta-analysis of effectiveness and complications. BJOG 2007;114:522-31.
12. Dursun P, Bildaci TB, Zeyneloglu HB, Kuscu E, Ayhan A. Transobturator tape operation is more effective in premenopausal women than in postmenopausal women with stress incontinence. Korean J Urol 2011;52:612-5.
13. Madjar S, Frischer Z, Nieder AM, Waltzer WC. Bladder wall abscess following midurethral sling procedure. Int Urogynecol J Pelvic Floor Dysfunct 2006;17:180-1.
14. Krauth JS, Rasoamiaramanana H, Bartela H BP, Grisard-Anafd M, Lienharte J, et al. Suburethral tape treatment of female urinary incontinence - morbidity assessement of the trans-obturator route and a new tape (I-STOP): a multi-centre experiment involving 602 cases. Eur Urol 2005;47:102-7.
15. Riva D, Sacca V, Tonta A, Casolati E, Luerti M, Banfet G. TVT versus TOT: a randomized study at 1 year follow up. Int Urogynecol J Pelvic Flor Dysfunct 2006:S93
16. Deval B, Ferchaux J, Berry R, Gambino S, Ciofu C, Rafii A, et al. Objective and subjective cure rates after trans-obturator tape (OBTAPE) treatment of female urinary incontinence. Eur Urol 2006;49:373-7.
17. Juma S, Brito CG. Transobturator tape (TOT): Two years follow-up. Neurourol Urodyn 2007;26:37-41.
18. Lo TS, Wang AC, Horng SG, Liang CC, Soong YK. Ultrasonographic and urodynamic evaluation after tension free vagina tape procedure (TVT). Acta Obstet Gynecol Scand 2001;80:65-70.
19. Porena M, Kocjancic E, Costantini E, Giannantonia A, Ranzonic S, Mearinia L, et al. Tension free vaginal tape vs transobturator tape as surgery for stress urinary incontinence: results of a multicentre randomised trial. . Neurourol Urodyn 2005;24:416-8.
20. Grise P, Droupy S, Saussine C, Ballanger P, Monneins F, Hermieu JF, et al. Transobturator tape sling for female stress incontinence with polypropylene tape and outside-in procedure: prospective study with 1 year of minimal follow-up and review of transobturator tape sling. Urology 2006;68:759-63.
21. Petros PE, Ulmsten UI. An integral theory of female urinary incontinence. Experimental and clinical considerations. Acta Obstet Gynecol Scand Suppl 1990;153:7-31.
22. Houwert RM, Venema PL, Aquarius AE, Bruinse HW, Roovers JP, Vervest HA. Risk factors for failure of retropubic and transobturator midurethral slings. Am J Obstet Gynecol 2009;201:202:1-8.
23. Rodriguez LV, de Almeida F, Dorey F, Raz S. Does Valsalva leak point pressure predict outcome after the distal urethral polypropylene sling? Role of urodynamics in the sling era. J Urol 2004;172:210-4.
24. Mellier G, Mistrangelo E, Gery L, Philippe C, Patrice M. Tension-free obturator tape (Monarc Subfascial Hammock) in patients with or without associated procedures. Int Urogynecol J Pelvic Floor Dysfunct 2007;18:165-72.

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The course and outcomes of complicated gallstone disease in pregnancy: Experience of a tertiary center

Gebelikte komplike safra taşı hastalığının seyri ve sonuçları: Tersiyer merkez deneyimi

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Abstract

Objective: To evaluate the course and outcomes of pregnant patients with complicated gallstone disease and to reveal the experience of a tertiary center.
Materials and Methods: The records of 92.567 patients were evaluated using searches for diagnoses with the terms of pregnant, pregnancy, gallstone, cholecystitis, cholangitis, choledocholithiasis, pancreatitis, and endoscopic retrograde cholangiopancreatography in pregnancy in the hospital database. Patients' age, week of gestation, parity, body mass index, definitive diagnosis, attack episodes, treatment modalities, and obstetric and neonatal complications were evaluated.
Results: Overall, 59 women were diagnosed as having complicated gallstone disease in pregnancy. Acute cholecystitis was the most commonly diagnosed complicated gallbladder disease (62.7%). Cholecystectomy was performed in 15 women during gestation. Perinatal outcomes were as follows: one (1.7%) maternal death, 4 (6.8%) preterm deliveries, 5 (8.5%) low-birth-weight fetuses, and 1 (1.7%) missed abortion were encountered. No fetal abnormalities were encountered.
Conclusion: A significant proportion of women experience biliary disease during pregnancy. Herein, we presented our clinical experience because the diagnosis, course, and management of complicated gallstone disease in pregnancy is complicated.
Keywords: Acute cholecystitis, acute pancreatitis, cholangitis, choledocholithiasis, pregnancy

Öz

Amaç: Komplike safra taşı hastalığı tanısı alan gebelerde hastalık seyri ve sonuçlarının değerlendirilmesi ve tersiyer merkezin klinik deneyiminin ortaya konması.
Gereç ve Yöntemler: Doksan iki bin beş yüz altmış yedi hastanın tıbbi kayıtları hastane veri-tabanında gebelik, gebe, safra taşı, kolesistit, kolanjit, koledokolithiazis, pankreatit ve gebelikte endoskopik retrograd kolanjiyopankreatografi tanılarının aranması ile bulundu. Hastaların yaşı, gebelik sayısı, parite, vücut kitle indeksi, kesin tanıları, atak sayısı, tedavi yöntemleri, obstetrik ve neonatal komplikasyonları değerlendirildi.
Bulgular: Toplam 59 kadın gebelikte komplike safra taşı hastalığı tanısı almıştı. Akut kolesistit gebelikte en sık görülen komplike safra taşı hastalığı oldu (%62,7). On beş gebeye kolesistektomi yapıldı. Perinatal sonuçlarda; bir anne ölümü (%1,7), 4 preterm doğum (%6,8), 5 düşük doğum ağırlıklı fetüs (%8,5) ve 1 missed abortusa (%1,7) rastlanmıştır. Fetal anomali hiçbir olguda rastlanmamıştır.
Sonuç: Kadınların önemli bir kısmı gebelik döneminde safra hastalığı yaşamaktadır. Komplike safra taşı hastalığı teşhisi, seyri ve yönetimi gebelik döneminde sıkıntılı olduğu için, bu çalışmada tek merkez klinik deneyimimiz aktarılmıştır.
Anahtar Kelimeler: Akut kolesistit, akut pankreatit, kolanjit, koledokolitiazis, gebelik

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Introduction

Gallstone disease is a common reason for non-gynecologic operations during pregnancy[1,2] and is the major non-obstetric cause for hospitalization in the first year postpartum[3]. A significant proportion of women experience biliary disease during pregnancy. Pregnancy may accentuate gallbladder stone formation. Alterations in hepatobiliary function occur during pregnancy to create a lithogenic environment. These changes include secretion of bile with increased amounts of cholesterol and decreased amounts of chenodeoxycholic acid and gallbladder stasis[4]. The prevalence of biliary sludge, gallstones, and biliary pancreatitis in pregnancy ranges from 5-36%, 2-11%, and 1/1000-3/10000, respectively[1,5-7]. In addition to the risks of symptomatic biliary disease on the mother and fetus, treatment approaches including surgery and conservative treatment bring their own risks and restrictions in pregnancy. Though recent guidelines have recommended laparoscopic cholecystectomy (LC) during pregnancy for all symptomatic gallstone disease[8,9], management of symptomatic disease during pregnancy has often been nonsurgical to avoid fetal and maternal harm[10]. However, this non-operative management leads to a very high rate of antepartum symptom recurrence[2,8]. The aim of the present study was to determine the course and outcomes of pregnant patients with complicated gallstone disease and to reveal the experience of a tertiary center.

Materials and Methods

The written and electronic medical records of 92.567 patients who were admitted to the Emergency Surgery Clinic in İstanbul University İstanbul Faculty of Medicine, between January 2010 and August 2015, were evaluated in this study. The medical records were reviewed using searches for diagnoses with the terms of pregnant, pregnancy, gallstone, cholecystitis, cholangitis, choledocholithiasis, pancreatitis, and endoscopic retrograde cholangiopancreatography (ERCP) in pregnancy in the hospital database. Patients diagnosed as having complicated gallstone disease were included in this study. Complicated gallstone disease was defined as acute cholecystitis, choledocholithiasis, cholangitis, and gallstone pancreatitis[3]. All diagnoses were made with a combination of medical history, physical examination, laboratory tests and imaging techniques such as [ultrasonography, and magnetic resonance cholangiopancreatography (MRCP)]. Diagnosis of acute cholecystitis was made when biliary pain was associated with the presence of both gallbladder lithiasis and inflammation. Acute biliary pancreatitis was diagnosed with the presence of gallbladder lithiasis, elevated serum amylase level, and presence of biliary pain. Choledocholithiasis was defined in the presence biliary symptoms, jaundice, abnormal liver function tests, and presence of gallbladder lithiasis. Common bile duct stones were confirmed with either ultrasonography or MRCP; these patients underwent ERCP. Cholangitis was diagnosed in the presence of fever and elevated acute phase reactants. LC and ERCP procedures were performed after explanation of the risks, complications, and alternatives. ERCPs were performed by general surgeons who were experienced with endoscopy using a Fujinon EPX-201 videoendoscope. Double-sided lead shielding was positioned above, below, and on both sides of the patient, covering the abdomen and pelvis in case there was a need for radiation. In all cases, selective cannulation was performed and confirmed by the aspiration and/or direct visualization of the bile. After cannulation of the common bile duct, a guide wire was passed and sphincterotomy was completed. Stones were extracted using a basket or balloon sweep[11]. LC was performed using a standard four-port technique. A hasson trocar was placed, and the abdominal cavity was insufflated with carbon dioxide, with a maximum insufflation pressure of 12 mmHg. Calot's triangle was identified and the cystic duct and cystic artery were clipped, taking care not to injure the common bile duct. The gallbladder was removed from the liver bed using diathermy. If clear exploration could not be provided using laparoscopy, laparotomic cholecystectomy was performed. Patients with pregnancy-related conditions that may be associated with epigastric pain including severe preeclampsia, hemolysis, elevated liver enzymes, and low platelet count syndrome, acute fatty liver, abruptio placentae, uterine rupture, and intraamniotic infection, and patients with primary sclerosing cholangitis, non-biliary pancreatitis, intrahepatic cholestasis, primary biliary cirrhosis, gallbladder and biliary duct tumors, drug-induced pancreatitis, gastroesophageal reflux, peptic ulcer disease, hepatitis, right-sided pneumonia, and appendicitis were excluded. Attack episode was defined as recurrence of disease after normal physical and laboratory findings. Patients were grouped according to the trimester in which the symptoms developed for the first time. Preterm delivery was defined as birth at <37 weeks of gestation. Low birth weight was defined as a birth weight of a live-born infant of less than 2500 gr. Patients' age, week of gestation, parity, body mass index (BMI), initial diagnosis at admission, definitive diagnosis, attack episodes, treatment modalities, and obstetric and neonatal complications were evaluated.

Statistical Analysis

Statistical analysis was performed using SPSS IBM 21 (IBM Co., Armonk, NY, USA). Descriptive analysis was performed including frequency, percentage, means, and standard deviation of the demographic features and disease history. The Shapiro-Wilk test was used to verify normality. The Kruskal-Wallis test was employed to analyze more than two variables in the study. $P<0.05$ was considered statistically significant.

Results

Overall, 59 women were diagnosed as having complicated gallstone disease in pregnancy. The demographic features of the patients are shown in Table 1. Thirteen (15.9%) of the patients presented in the first trimester, 25 (30.5%) patients in the second, and 21 (25.6%) patients presented in the

third trimester. Table 1 summarizes the distribution of cases throughout pregnancy. Fifty-one (86.4%) of the 59 patients had one attack episode and 6 (10.2%) patients were admitted to hospital twice. Two (3.4%) patients had 3 attack episodes (Table 2).

Acute cholecystitis was the most commonly diagnosed complicated gallstone disease in pregnancy; 37 patients were diagnosed as having acute cholecystitis during pregnancy (Table 3).

ERCPs were performed in 4 patients and the procedure was conducted without radiation. Three of the 4 patients opted for laparoscopic surgery. Cholecystectomy was performed in 15 pregnant women; 9 (60%) patients underwent surgery during the second trimester, 1 (6.6%) patient had surgery in the first trimester, and the remainder (n=5) (33.3%) underwent surgery in the third trimester. Laparotomy was performed in 1 patient in the third trimester due to inadequate exploration during laparoscopy.

Perinatal outcomes are summarized in Table 4. Four of the 59 pregnant women had preterm delivery. Two of these had undergone surgery and the remainder were treated conservatively. One of 59 pregnant women had a missed abortion (8 weeks of

Table 1. Demographic features of the patients and distribution of cases throughout pregnancy

		n (%)	Mean age	GWD	Parity	BMI
Pregnant	1st trimester	13 (15.9)	27±4	9.35±2.44	3 (1-6)	27.35±5.66
	2nd trimester	25 (30.5)	29±6	19.04±3.43	2 (1-4)	29.75±5.86
	3rd trimester	21 (25.6)	28±5	30.52±4.60	3 (1-5)	31.73±5.98
	Total	59	28±5	20.99±8.85	2 (1-6)	29.61±5.83

GWD: Gestational week at diagnosis, BMI: Body mass index, n: Number of patients

Table 2. Attack episodes

Attack episodes	n	%
1	51	86.4
2	6	10.2
3	2	3.4
Total	59	100

n: Number of patients

Table 3. Distribution of patients according to diagnosis and surgical intervention

Diagnosis	Pregnancy n (%)	Cholecystectomized pregnant patients
Acute cholecystitis	37 (62.7%)	9
Acute pancreatitis	15 (25.4%)	3
Choledocholithiasis	4 (6.8%)	2
Cholangitis	3 (5%)	1

n: Number of patients

Table 4. Perinatal outcomes of the cases

Diagnosis	n	(%)	Cholecystectomy patients	Conservatively treated patients
Preterm delivery	4	(6.8%)	2 (3.4%)	2 (3.4%)
Missed abortion	1	(1.7%)	-	1 (1.7%)
Low birth weight	5	(8.5%)	2 (3.4%)	3 (5 %)
Gross fetal anomaly	0	-	-	-
Maternal death	1	(1.7%)	-	1 (1.7%)

n: Number of patients

gestation). That patient had been treated conservatively. Five infants had a low birth weight. No gross fetal anomalies were encountered in either the conservatively- or surgically-treated patients. One maternal death was encountered. This patient had severe acute pancreatitis.

Discussion

Although some pregnant patients experience uncomplicated cholelithiasis, an important proportion develop complicated gallstone disease defined as acute cholecystitis, choledocholithiasis, cholangitis, and gallstone pancreatitis[3]. It is widely understood that symptomatic gallstone disease in pregnancy is related with increased mortality risk for both the mother and fetus and may result in complications including spontaneous abortion, fetal abnormalities, preterm labor, and even death[2,5,7]. The management of symptomatic biliary disease during pregnancy has often been nonsurgical to avoid fetal and maternal harm[10], but ironically, this results in a high rate of antepartum symptom recurrence[2,8,9]. Although laparoscopy is known to be safe in the second trimester, studies have reported the risk of preterm labor or spontaneous abortion with LC[12,13].

There is agreement concerning the security of LC during the second trimester of pregnancy and some physicians also extend the indication to the first and third trimester[12,14-17]. Recent guidelines recommended LC during pregnancy for all symptomatic gallstone disease[8,9] and laparoscopic treatment of acute abdominal disease has the same indications in pregnant and non-pregnant patients[18]. Studies reporting uterine injury during trocar placement, increased risk of preterm labor and spontaneous abortion with LC exist, even though they were performed in the second trimester[12,13]. The rate of preterm labor is 0-20% for LC[19-23]. Fetal mortality rates following LC range from 0 to 5.2%[19-23]. In our study, the rate of preterm labor was 3.4% and fetal mortality was not encountered after LC. Symptomatic gallstone disease has been related with increased mortality risk for the mother and fetus, besides the risk of interventions in pregnancy[7]. Complications including spontaneous abortion, fetal abnormalities, preterm labor, and even fetal and maternal death may occur. In our study, 1 missed abortion, 1 maternal death, 2 preterm deliveries, 3 low-birth-weight fetuses, and no fetal abnormalities were encountered in conservatively-treated patients. A case series in the literature reported that the most common reasons for biliary surgery during pregnancy were biliary colic in 70% of cases, followed by acute cholecystitis in 20%, choledocholithiasis in 7%, and acute biliary pancreatitis in the remaining 3% of cases[14]. In our study, acute cholecystitis was the most commonly diagnosed complicated gallbladder disease in pregnancy; 37 (62.7%) patients were diagnosed as having acute cholecystitis during pregnancy.

There is a very high rate of antepartum symptom recurrence with nonsurgical management of symptomatic biliary disease during pregnancy[2,8,10]. It was reported that non-operative management of symptomatic cholelithiasis in pregnancy was associated with frequent hospitalizations[24,25]. Recurrence rates after conservative treatment range between 40-92%. Recurrence of biliary pancreatitis was observed in 50% of patients after conservative treatment[24]. A higher incidence of preterm labor for patients with conservative versus surgical treatment, with a clear relation with symptom recurrence was reported[22]. In our study, 6 (10.2%) patients had 2 attack episodes and 2 (3.4%) were admitted to hospital on three further occasions.

ERCP is an important therapeutic option in patients with biliary and pancreatic disease. ERCP is a very effective way to extract common bile duct stones[11]. In the literature, it was concluded that ERCP could be performed safely during pregnancy. On the other hand, a lower rate of term pregnancy, higher rate of preterm delivery, and low birth weight were more common when interventions were required during the first trimester[26]. In our study, ERCP was performed in 4 patients. Three out of the 4 patients chose LC.

We present our clinical experience because the diagnosis, course, and management of complicated gallstone disease is complicated. We aimed to determine the outcomes of pregnant patients. As a new thought, biliary tract screening by sonographic examination may be recommended before pregnancy, and LC prior to pregnancy may be suggested to prevent complications related to gallstones during gestation. It might be especially considered for pregnant patients with a high BMI and a history of multiple small stones in the gallbladder. However, further randomized controlled trials are required before this idea can be fully supported. There are some limitations of this study. This study had a retrospective design and the patient population was small; further studies with greater patient populations will highlight possible missing comments.

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Ethics

Ethics Committee Approval: Retrospective study, Informed consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contribution

Surgical and Medical Practices: Mehmet İlhan, Kayıhan Günay, Cemalettin Ertekin, Concept: Mehmet İlhan, Gülşah İlhan, Kayıhan Günay, Design: Mehmet İlhan, Gülşah İlhan, Kayıhan Günay, Data Collection or Processing: Mehmet İlhan, Ali Fuat Kaan Gök, Analysis or Interpretation: Mehmet İlhan, Gülşah İlhan, Literature Search: Mehmet İlhan, Gülşah İlhan, Writing: Mehmet İlhan, Gülşah İlhan.

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References

1. Sungler P, Heinerman PM, Steiner H, Waclawiczek HW, Holzinger J, Mayer F, et al. Laparoscopic cholecystectomy and interventional endoscopy for gallstone complications during pregnancy. Surg Endosc 2000;14:267-71.
2. Date RS, Kaushal M, Ramesh A. A review of the management of gallstone disease and its complications in pregnancy. Am J Surg 2008;196:599-608.
3. Ko CW. Risk factors for gallstone-related hospitalization during pregnancy and the postpartum. Am J Gastroenterol 2006;101:2263-8.
4. Gilo NB, Amini D, Landy HJ. Appendicitis and cholecystitis in pregnancy. Clin Obstet Gynecol 2009;52:586-96.
5. Mendez-Sanchez N, Chavez-Tapia NC, Uribe M. Pregnancy and gallbladder disease. Ann Hepatol 2006;5:227-30.
6. Ko CW, Beresford SA, Schulte SJ, Matsumoto AM, Lee SP. Incidence, natural history, and risk factors for biliary sludge and stones during pregnancy. Hepatology 2005;41:359-65.
7. Valdivieso V, Covarrubias C, Siegel F, Cruz F. Pregnancy and cholelithiasis: pathogenesis and natural course of gallstones diagnosed in early puerperium. Hepatology 1993;17:1-4.
8. Pearl J, Price R, Richardson W, Fanelli R, Society of American Gastrointestinal Endoscopic S. Guidelines for diagnosis, treatment, and use of laparoscopy for surgical problems during pregnancy. Surg Endosc 2011;25:3479-92.
9. Soper NJ. SAGES' guidelines for diagnosis, treatment, and use of laparoscopy for surgical problems during pregnancy. Surg Endosc 2011;25:3477-8.
10. Maringhini A, Ciambra M, Baccelliere P, Raimondo M, Orlando A, Tine F, et al. Biliary sludge and gallstones in pregnancy: incidence, risk factors, and natural history. Ann Intern Med 1993;119:116-20.
11. Agcaoglu O, Ozcinar B, Gok AF, Yanar F, Yanar H, Ertekin C, et al. ERCP without radiation during pregnancy in the minimal invasive world. Arch Gynecol Obstet 2013;288:1275-8.
12. Glasgow RE, Visser BC, Harris HW, Patti MG, Kilpatrick SJ, Mulvihill SJ. Changing management of gallstone disease during pregnancy. Surg Endosc 1998;12:241-6.
13. Graham G, Baxi L, Tharakan T. Laparoscopic cholecystectomy during pregnancy: a case series and review of the literature. Obstet Gynecol Surv 1998;53:566-74.
14. Ghumman E, Barry M, Grace PA. Management of gallstones in pregnancy. Br J Surg 1997;84:1646-50.
15. Patel SG, Veverka TJ. Laparoscopic cholecystectomy in pregnancy. Curr Surg 2002;59:74-8.
16. Eichenberg BJ, Vanderlinden J, Miguel C, Bianchi C, Robles A, McLarty R, et al. Laparoscopic cholecystectomy in the third trimester of pregnancy. Am Surg 1996;62:874-7.
17. Schwartzberg BS, Conyers JA, Moore JA. First trimester of pregnancy laparoscopic procedures. Surg Endosc 1997;11:1216-7.
18. Reedy MB, Galan HL, Richards WE, Preece CK, Wetter PA, Kuehl TJ. Laparoscopy during pregnancy. A survey of laparoendoscopic surgeons. J Reprod Med 1997;42:33-8.
19. Rollins MD, Chan KJ, Price RR. Laparoscopy for appendicitis and cholelithiasis during pregnancy: a new standard of care. Surg Endosc 2004;18:237-41.
20. Abuabara SF, Gross GW, Sirinek KR. Laparoscopic cholecystectomy during pregnancy is safe for both mother and fetus. J Gastrointest Surg 1997;1:48-52.
21. Curet MJ, Allen D, Josloff RK, Pitcher DE, Curet LB, Miscall BG, et al. Laparoscopy during pregnancy. Arch Surg 1996;131:546-50.
22. Lu EJ, Curet MJ, El-Sayed YY, Kirkwood KS. Medical versus surgical management of biliary tract disease in pregnancy. Am J Surg 2004;188:755-9.
23. Cosenza CA, Saffari B, Jabbour N, Stain SC, Garry D, Parekh D, et al. Surgical management of biliary gallstone disease during pregnancy. Am J Surg 1999;178:545-8.
24. Jorge AM, Keswani RN, Veerappan A, Soper NJ, Gawron AJ. Non-operative management of symptomatic cholelithiasis in pregnancy is associated with frequent hospitalizations. J Gastrointest Surg 2015;19:598-603.
25. Swisher SG, Schmit PJ, Hunt KK, Hiyama DT, Bennion RS, Swisher EM, et al. Biliary disease during pregnancy. Am J Surg 1994;168:576-9; discussion 80-1.
26. Tang SJ, Mayo MJ, Rodriguez-Frias E, Armstrong L, Tang L, Sreenarasimhaiah J, et al. Safety and utility of ERCP during pregnancy. Gastrointest Endosc 2009;69:453-61.

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Hysteroscopy: A necessary method for detecting uterine pathologies in post-menopausal women with abnormal uterine bleeding or increased endometrial thickness

Histeroskopi: Anormal uterin kanaması olan veya artmış endometrial kalınlık tanısı konmuş post-menopozal kadınlarda uterin patolojilerini tespit etmek için gerekli bir yöntem

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Abstract

Objective: To investigate the histologic and hysteroscopic findings of post-menopausal women with uterine bleeding and asymptomatic women with increased endometrial thickness equal or more than 5 mm.

Materials and Methods: This cross-sectional study was performed between May 2014 and June 2015 on 110 post-menopausal women aged 40-82 years. The women were divided into two groups: Women with abnormal uterine bleeding (AUB group) and asymptomatic women with increased endometrial thickness (asymptomatic group).

Results: Among the participants, 67 women had AUB and 43 women were asymptomatic. In the AUB group sensitivity, specificity, and positive and negative predictive values of hysteroscopy for normal findings were 98%, 100%, 100% and 90%, respectively. In the asymptomatic group, the same parameters were 98%, 100%, 100% and 85%, respectively. The sensitivity, specificity, and positive and negative predictive values of hysteroscopy for polyps and myomas were 100%. Also, the sensitivity, specificity, and positive and negative predictive values were 100% in hyperplasia cases found during hysteroscopy in both groups.

Conclusion: Increased endometrial thickness in postmenopausal women with or without AUB is mostly due to benign lesions such as polyps and submucosal myomas. Hysteroscopy is a safe and reliable method for evaluating and treating these lesions.

Keywords: Abnormal uterine bleeding, endometrial thickness, post-menopause, hysteroscopy, endometrial biopsy

Öz

Amaç: Uterin kanaması olan post-menapozal kadınlarda ve artmış endometrial kalığı 5 mm ve üzeri olan asemptomatik olan kadınlarda histolojik ve histeroskopik bulguları incelemek.

Gereç ve Yöntemler: Bu kesitsel çalışma Mayıs 2014 ve Haziran 2015 yılları arasında, yaşları 40 ve 82 arasında olan 110 post-menopozal kadın üzerinde gerçekleştirilmiştir. Kadınlar iki gruba ayrılmıştır: Anormal uterin kanaması (AUK grubu) olan kadınlar ve artmış endometrial kalınlığı olan asemptomatik kadınlar (asemptomatik grup).

Bulgular: Katılımcılar arasından 67 kadında AUK mevcuttu ve 43 kadın asemptomatikti. AUK grubunda, normal bulgular için sensitivite, özgünlük, pozitif ve negatif belirleyicilik değerleri sırasıyla %98, %100, %100 ve %90 idi. Asemptomatik grupta, aynı değerler sırasıyla %98, %100, %100 ve %85 olarak bulundu. Polipler ve miyomlar için histeroskopinin sensitivite, özgünlük, pozitif ve negatif belirleyicilik değerleri %100 olarak tespit edildi. Ayrıca, her iki grupta histeroskopi ile tespit edilen hiperplazi olgularında sensitivite, özgünlük, pozitif ve negatif belirleyicilik değerleri %100 idi.

Sonuç: AUK olan veya olmayan post-menopozal kadınlarda artmış endometrial kalınlık çoğunlukla polipler ve submukozal miyomlar gibi benign lezyonlardan kaynaklanmaktadır. Bu lezyonları değerlendirmek ve tedavi etmek için histeroskopi güvenli ve güvenilir bir yöntemdir.

Anahtar Kelimeler: Anormal uterin kanama, endometrial kalınlık, post-menopoz, histeroskopi, endometrial biyopsi

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Introduction

Abnormal uterine bleeding (AUB) is as any kind of uterine bleeding in terms of duration, frequency, and volume. In postmenopausal women, women without a menstrual cycle for one year, any bleeding is abnormal. Postmenopausal bleeding has different causes including endometrial atrophy, polyps, myomas, endometrial hyperplasia, and endometrial carcinoma. Endometrial carcinoma is the most common malignancy of genital organs in women in developed countries. About 80% of endometrial cancers in post-menopausal women occur at ages of 50 to 65 years[1]. On the other hand 10% to 15% of women with post-menopausal bleeding have endometrial cancer[2,3]. Therefore, it is important to evaluate AUB in postmenopausal women very carefully. Measurement of endometrial line thickness by transvaginal sonography (TVS) is the first step to determine the need for further evaluations to rule out malignancy in these patients[4]. In case of endometrial thickness more than 4-5 mm in TVS of patients with postmenopausal bleeding, more evaluation is required to rule out cancer. Considering these values, the incidence of endometrial cancer with measurements thinner than this cut-off point is less than 1%[5,6]. There is no agreement on the described threshold of endometrial thickness to differentiate between normal and abnormal endometrial pathologies in postmenopausal women without bleeding[7,8]. Some guidelines and researchers have suggested that asymptomatic post-menopausal women with endometrial thickness of 4-5 mm or more do not need endometrial biopsy unless AUB occurs[9,10]. However, some researchers believe that postmenopausal endometrial thickness represents an increased risk of malignancy or other underlying pathologies, such as hyperplasia, polyps or myomas, and should be evaluated[11]. Hysteroscopy is a precise, easy, and quick method to assess and identify any intrauterine pathology with which we are able to observe the whole endometrial cavity and take adequate biopsies of any suspicious lesions. This procedure has recently been suggested as the best available method to evaluate the uterine cavity of women with endometrial line thickness with or without AUB[12,13]. Another advantage of hysteroscopy is the "see and treat" method in which simultaneous real-time macroscopic diagnosis of benign lesions and resection can be made[1,14]. This study was designed to investigate and compare the histologic and hysteroscopic findings of post-menopausal women with AUB and asymptomatic women with increased endometrial thickness.

Materials and Methods

This cross-sectional study was performed between May 2014 and June 2015 on post-menopausal women who were referred to a center in Tehran because of having endometrial thickness equal or more than 5 mm in TVS, with or without AUB. They were divided into two groups: women with AUB group and asymptomatic women with increased endometrial thickness (asymptomatic group). Menopause was defined as the absence of menstrual periods for more than 12 months. The study protocol was approved by our university's ethics committee.

The inclusion criteria were: (1) being menopausal; (2) aged 40-82 years; (3) having uterine bleeding; and (4) having increased endometrial thickness (≥5 mm). The exclusion criteria were: (1) using hormonal replacement therapy, anticoagulants or selective estrogen receptor modulators; (2) having vaginal bleeding with a known cause in the vagina or cervix; (3) having any adnexal abnormality in TVS; (4) having any kind of cancer; and (5) being menopausal because of ovarian surgery. All participants signed an informed consent form before participating in this study. Transvaginal ultrasound was done for all participants. Endometrial line thickness was measured at the thickest part in the longitudinal plan of TVS with 7.5 MHz vaginal probe. The cut-off value of endometrial thickness was 5 mm or more. Adnexal regions also were assessed by TVS. If any mass or abnormality was observed in the adnexa, the woman was excluded from the study[1,15]. Of the 148 women who were referred to our center in the defined period, 110 women met the inclusion criteria. Among them, 67 women had AUB group and 47 women were asymptomatic with endometrial thickness (asymptomatic group).

Hysteroscopy was conducted in an outpatient setting with a 3.5-mm Storz hysteroscope and 30 degrees view by an operator with 8 years of experience in performing hysteroscopy. The media was normal saline and hysteroscopy was performed with or without complete or local anesthesia. The whole endometrial level and cavity were precisely and systematically evaluated using hysteroscopy. All findings were recorded accurately.

Hysteroscopic findings were defined precisely based on the specific findings detected during the procedure. Normal hysteroscopic findings included a normal, non-vascular smooth level. Abnormal findings included polyps, submucosal myomas, endometrial hyperplasia, and endometrial cancer[16].

Hyperplasic endometrium was defined as endometrium that was highly vascular, thick, and polypoid in appearance. Endometrial grooves became visible whenever it was pressed by the hysteroscope. Presence of abnormal vascular pattern and irregular fragile polypoid tissue with bleeding necrosis was defined as a sign of endometrial carcinoma[17]. Endometrial biopsy was performed for all participants with intrauterine lesions. Punch biopsies were conducted in women with atrophic endometrium who had no pathology in hysteroscopy. In women with pre-malignant or malignant lesions, targeted and random biopsies were performed. In women with polyps or myomas, the lesions were all resected using scissors or resectoscope, respectively. The biopsies were immediately placed in 10% formaldehyde and sent to the pathology laboratory. The pathologist knew nothing of the hysteroscopic findings. Histologic findings were defined as the final exact diagnosis standard of the endometrial pathology. The pathologic findings between the two groups and the percentages of each finding were analyzed. The hysteroscopy's predictive value in endometrial lesions' diagnosis was assessed based on

the sensitivity, specificity, and positive and negative predictive values[18,19].

Statistical Analysis

Categorical and continuous variables are summarized as number (percentage) and mean, respectively. Hysteroscopy was considered as a screening test and endometrial biopsy as a standard. Data analysis was performed using the Statistical Package for Social Sciences (SPSS) version 20 (Chicago, IL, USA) by calculating sensitivity, specificity, and positive and negative predictive values.

Results

This study was conducted on post-menopausal women with a mean age of 57 years. Of the 110 participants with endometrial thickness equal or more than 5 mm, 67 (60.9%) had AUB. All 110 patients underwent hysteroscopy and endometrial biopsy. The hysteroscopic findings were categorized into five groups: normal, polyps, myomas, hyperplasia, and carcinoma (Table 1).

Table 1. Hysteroscopic findings of our study groups

Hysteroscopic findings	AUB group	Asymptomatic group	Total
Normal	10	7	15.5%
Polyp	30	23	48.2%
Myoma	13	7	18.2%
Hyperplasia	11	5	14.5%
Carcinoma	3	1	3.6%
Total	67 (60.9%)	43 (39.09)	100%

AUB: Abnormal uterine bleeding

We compared the hysteroscopy and pathology results of all participants. Among 17 women who had normal hysteroscopy in both groups, one woman in each group had simple hyperplasia in histopathology and the other had atrophy (atrophy in our classification was part of normal results) (Table 2).

The most common finding on hysteroscopic evaluation was endometrial polyps in both groups (44.1% and 53.5% in AUB and asymptomatic groups, respectively). There were a total of 55 polyps and 20 myomas in both groups, which were confirmed by histopathology. Hyperplasia was found in 16 participants (11 and 5 in AUB and asymptomatic groups, respectively). This was confirmed with histology. Eleven cases were simple hyperplasia and five were complex or atypical hyperplasia. Three women in the AUB group and one in the asymptomatic group were suspected of having carcinoma in the hysteroscopy. Regarding the AUB group, the sensitivity, specificity, and positive and negative predictive values of the hysteroscopic view for finding normal results were 98%, 100%, 100% and 90%, respectively. In the asymptomatic group these parameters were 98%, 100%, 100% and 85%, respectively (Table 3). The sensitivity, specificity, and positive and negative predictive values of hysteroscopy for polyps and myomas were 100%. The sensitivity, specificity, and positive and negative predictive values were 100% for detecting hyperplasia with hysteroscopy in both groups. The sensitivity, specificity, and positive and negative predictive values of hysteroscopy for detecting carcinoma in the AUB group were 100%, 97%, 33% and 100%, respectively (Table 3). All lesions occupying the uterus (53 polyps and 20 uterine myomas) were diagnosed using hysteroscopy.

Discussion

The average of life expectancy for women has increased in recent years because of improved quality of life. Also, the

Table 2. Comparison of the results of hysteroscopy and histopathologic findings of abnormal uterine bleeding and asymptomatic groups

Hysteroscopy	Histopathology					
	Polyp	Myoma	Simple hyperplasia	Complex or atypical	Carcinoma	Atrophy or not satisfactory
AUB group						
Normal	-	-	1	-	-	9
Polyp	30	-	-	-	-	-
Myoma	-	13	-	-	-	-
Hyperplasia	-	-	8	3	-	-
Carcinoma	-	-	-	2	1	-
Asymptomatic group						
Normal	-	-	1	-	-	6
Polyp	23	-	-	-	-	-
Myoma	-	7	-	-	-	-
Hyperplasia	-	-	3	2	-	-
Carcinoma	-	-	-	1	-	-

AUB: Abnormal uterine bleeding

number of women older than 60 years is increasing. In spite of the absence of vaginal bleeding, these women may still have uterine pathologies such as endometrial hyperplasia, polyps, uterine fibroids, adenomiosis or even endometrial cancer, some of which can be malignant. Up to now, there is no common agreement regarding the clinical management of increased endometrial line thickness in post-menopausal women.

In our study, the common cause of endometrial thickening and AUB was endometrial polyp, which is consistent with other studies[1,20-24]. Fortunately, polyps were not histologically malignant in our patients and this finding is in agreement with Loiacono et al.[24] study. Elfayomy et al.[2] showed that about 20% of polyps had malignant components hidden in their stem or center despite normal endometrial pathology in endometrial biopsy. Therefore, the authors suggested performing polypectomy via hysteroscopy in such women. On the other hand, 20 women of our study who only had increased endometrial thickness in TVS had submucosal myomas. Among them, 13 women had AUB and seven were asymptomatic. Therefore, we suggest that hysteroscopy be performed in all postmenopausal women with endometrial thickness ≥5 mm with or without AUB because of the successful resection of all polyps and sub-mucosal myomas without complications in these women[1,17,24,25]. It seems that more evaluations are needed in such cases because 86% of asymptomatic women with increased endometrial line thickness had underlying pathologic findings. This is in agreement with the studies of Loiacono et al.[24] and Hartman et al.[15].

In a study by Korkmazer et al.[20] on post-menopausal women with increased endometrial thickness, all intra-uterine lesions including polyps and submucosal myomas were diagnosed only via hysteroscopy. Curettage was not able to detect all lesions in their study; 25 of 93 women with atrophic endometrium had endometrial polyp in hysteroscopy and direct biopsy. Also, Lee et al.[25] compared biopsies obtained by curettage and hysteroscopy in post-menopausal women with bleeding. The authors concluded that performing curettage may not be reliable enough for evaluating endometrial pathology and suggested that endometrial biopsy with hysteroscopy must become the standard of diagnosis in these women. If endometrial biopsy is performed blindly, the detection of endometrial polyps or submucosal myomas might be missed. This leads to under diagnosis of this pathology during menopause. Therefore, the possibility of missing the underlying pathology will be eliminated by doing hysteroscopy[20,26,27].

In our study, there was more endometrial hyperplasia in the AUB group than in the asymptomatic group (16% vs. 11.6%, respectively). Hysteroscopy in these patients enabled us to take targeted biopsies under direct vision. According to some studies, hysteroscopy did not have the desirable sensitivity compared with endometrial biopsy in women with endometrial hyperplasia. Thus, it was suggested to take endometrial biopsy under direct visualization during hysteroscopy[2,28,29]. The sensitivity, specificity, and positive and negative predictive values of hysteroscopy in diagnosing polyps, myomas, and endometrial hyperplasia were 100% in both groups. This finding is not in agreement with the diagnostic capability of hysteroscopy without biopsy in some studies[2,30,31]. Loiacono et al.[24] diagnosed three women with endometrial carcinoma while studying women who had normal hysteroscopic findings. The sensitivity and positive predictive value of hysteroscopy decreased to 63% and 77% in their malignant cases. Our findings showed the same decrease in positive predictive value of hysteroscopy, which is consistent with their study. A limitation of our study was the small number of participants. Thus, the hysteroscopic values for endometrial malignancies' diagnosis could not be assessed in the asymptomatic group. Of the women in AUB group, 1.5% had histologically confirmed endometrial cancer, and 5% had atypical or complex hyperplasia. However, the positive predictive value of hysteroscopy for diagnosing carcinoma was 35%. In some studies, the percentage of cancer in asymptomatic women with endometrial thickness more than 5 mm was 0.5-1.4%[32-35].

In a study by Elfayomy et al.[2] endometrial carcinoma was not reliably detected with hysteroscopy. In their study, 7 of 14 women (16.9%) with endometrial cancer had suspicious findings in hysteroscopy, and no abnormality was found in the other half. According to the authors, the specificity

Table 3. Sensitivity, specificity, and positive and negative predictive values of hysteroscopy

Study groups	Hysteroscopic findings	Sensitivity	Specificity	Positive predictive value	Negative predictive value
AUB group	Normal	98%	100%	100%	90%
	Polyp-myoma	100%	100%	100%	100%
	Endometrial hyperplasia	100%	100%	100%	100%
	Carcinoma	100%	97%	33%	100%
Asymptomatic group	Normal	98%	100%	100%	85%
	Polyp-myoma	100%	100%	100%	100%
	Endometrial hyperplasia	100%	100%	100%	100%

AUB: Abnormal uterine bleeding

of hysteroscopy without biopsy was low in diagnosing endometrial cancer. This finding has been reported in other studies too[28,36]. Therefore, it is recommended to perform a biopsy even if hysteroscopy finds no abnormality to increase the validity of hysteroscopy in diagnosing endometrial hyperplasia and cancer in post-menopausal women with bleeding or with endometrial line thickness of 5 mm or more in TVS. In our study, we compared the results of hysteroscopy with the results of histopathology in post-menopausal women with AUB or endometrial thickness of 5 mm or more. According to our findings and other studies, endometrial thickness is often due to the presence of benign lesions such as polyps and submucosal myomas[2,7,24]. Our study showed that hysteroscopy is a safe and reliable method for evaluating benign endometrium lesions. In our study, all studied women had a histologic confirmation of their diagnosis, which makes our findings a desirable and optimal reference. Hysteroscopy is more accurate than transvaginal ultrasound or dilatation and curettage in the diagnosis of endometrial polyps and other space-occupying endometrial lesions in post-menopausal women[20,37]. Considering the failure rate of ultrasound or dilatation and curettage in detecting some endometrial lesions, evaluation of the endometrial cavity by direct visualization is critical in diagnosing space-occupying lesions in post-menopausal women.

Conclusion

In contrast to some studies that state that doing hysteroscopy in asymptomatic post-menopausal women with increased endometrial thickness is not cost-efficient[34,36,38] the present study showed that hysteroscopy is a safe and reliable procedure for evaluating benign lesions of endometrium such as polyps or submucosal myomas.

In order to rule out endometrial hyperplasia and cancer in postmenopausal women with bleeding or asymptomatic women with endometrial thickness, performing hysteroscopy and taking endometrial biopsies is recommended even if no lesion has been found. Further long-term prospective studies with more participants are necessary to find the optimum endometrial thickness in asymptomatic postmenopausal women.

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Ethics

Informed Consent: All participants signed an informed consent before participating in this study.

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Authorship Contributions

Surgical and Medical Practices: Fatemeh Sarvi, Marzieh Aghahosseini, Concept: Ashraf Alleyassin, Design: Marzieh Ghasemi, Fatemeh Sarvi, Data Collection or Processing: Fatemeh Sarvi, Sima Gity, Analysis or Interpretation: Marzieh Ghasemi, Literature Search: Marzieh Ghasemi, Sima Gity, Fatemeh Sarvi, Writing: Marzieh Ghasemi, Sima Gity.

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References

1. Merrill RM, Fugal S, Novilla LB, Raphael MC. Cancer risk associated with early and late maternal age at first birth. Gynecol Oncol 2005;96:583-93.
2. Elfayomy AK, Habib FA, Elkablawy MA. Role of hysteroscopy in the detection of endometrial pathologies in women presenting with postmenopausal bleeding and thickened endometrium. Arch Gynecol Obstet 2012;285:839-43.
3. Sousa R, Silvestre M, Almeida e Sousa L, Falcao F, Dias I, Silva T, et al. Transvaginal ultrasonography and hysteroscopy in postmenopausal bleeding: a prospective study. Acta Obstet Gynecol Scand 2001;80:856-62.
4. Smith-Bindman R, Kerlikowske K, Feldstein VA, Subak L, Scheidler J, Segal M, et al. Endovaginal ultrasound to exclude endometrial cancer and other endometrial abnormalities. JAMA 1998;280:1510-7.
5. Epstein E. Management of postmenopausal bleeding in Sweden: a need for increased use of hydrosonography and hysteroscopy. Acta Obstet Gynecol Scand 2004;83:89-95.
6. Goldstein RB, Bree RL, Benson CB, Benacerraf BR, Bloss JD, Carlos R, et al. Evaluation of the woman with postmenopausal bleeding: Society of Radiologists in Ultrasound-Sponsored Consensus Conference statement. J Ultrasound Med 2001;20:1025-36.
7. Kalampokas T, Gregoriou O, Grigoriadis C, Iavazzo C, Zervakis A, Sofoudis C, et al. Comparing transvaginally defined endometrial thickness with hysteroscopic and histopathologic findings in asyptomatic postmenopausal women. Eur J Gynaecol Oncol 2012;33:508-11.
8. Dreisler E, Sorensen SS, Ibsen PH, Lose G. Value of endometrial thickness measurement for diagnosing focal intrauterine pathology in women without abnormal uterine bleeding. Ultrasound Obstet Gynecol 2009;33:344-8.
9. Wolfman W, Leyland N, Heywood M, Singh SS, Rittenberg DA, Soucy R, et al. SOGC Clinical Practice Guideline No. 249. . 2010;32:990-9.
10. Goldstein SR. Modern evaluation of the endometrium. Obstet Gynecol 2010;116:168-76.
11. Schmidt T, Breidenbach M, Nawroth F, Mallmann P, Beyer IM, Fleisch MC, et al. Hysteroscopy for asymptomatic postmenopausal women with sonographically thickened endometrium. Maturitas 2009;62:176-8.
12. Grimes DA. Diagnostic dilation and curettage: a reappraisal. Am J Obstet Gynecol 1982;142:1-6.
13. Campaner AB, Piato S, Ribeiro PAG, Aoki T, Nadais RF, Prado RAA. Hysteroscopic findings in postmenopausal women with endometrial thickening diagnosed by transvaginal ultrasound. Rev Bras Ginecol Obstet 2004;26.
14. Lalchandani S, Phillips K. Evaluation of endometrial cavity-investigation options., Reviews in Gynaecological Practice. Reviews in Gynaecological Practice 2003;3:165-70.
15. Hartman A, Wolfman W, Nayot D, Hartman M. Endometrial thickness in 1,500 asymptomatic postmenopausal women not on hormone replacement therapy. Gynecol Obstet Invest 2013;75:191-5.

16. Lasmar RB, Dias R, Barrozo PR, Oliveira MA, Coutinho Eda S, da Rosa DB. Prevalence of hysteroscopic findings and histologic diagnoses in patients with abnormal uterine bleeding. Fertil Steril 2008;89:1803-7.
17. Ben-Yehuda OM, Kim YB, Leuchter RS. Does hysteroscopy improves upon the sensitivity of dilatation and curettage in the diagnosis of endometrial hyperplasia or carcinoma? 1998;68:4-7.
18. Lilienfeld DE, Stolley PD. Experimental epidemiology: randomized clinical trials. In: Foundation of epidemiology. Vol 8. Oxford, Oxford University Press; 1994;155-178.
19. Irwig L, Macaskill P, Glasziou P, Fahey M. Meta-analytic methods for diagnostic test accuracy. J Clin Epidemiol 1995;48:119-30.
20. Korkmazer E, Solak N, Ustunyurt E. Hysteroscopic assessment of postmenopausal endometrial thickening. Prz Menopauzalny 2014;13:330-3.
21. Gan DE, Jawan RA, Moy FM. Concordance between hysteroscopic impression and endometrial histopathological diagnosis. Prev Med 2013;57:S21-3.
22. Loizzi V, Bettocchi S, Vimercati A, Ceci O, Rossi C, Marello F, et al. Hysteroscopic evaluation of menopausal women with endometrial thickness of 4 mm or more. J Am Assoc Gynecol Laparosc 2000;7:191-5.
23. Litta P, Merlin F, Saccardi C, Pozzan C, Sacco G, Fracas M, et al. Role of hysteroscopy with endometrial biopsy to rule out endometrial cancer in postmenopausal women with abnormal uterine bleeding. Maturitas 2005;50:117-23.
24. Loiacono RM, Trojano G, Del Gaudio N, Kardhashi A, Deliso MA, Falco G, et al. Hysteroscopy as a valid tool for endometrial pathology in patients with postmenopausal bleeding or asymptomatic patients with a thickened endometrium: hysteroscopic and histological results. Gynecol Obstet Invest 2015;79:210-6.
25. Lee DO, Jung MH, Kim HY. Prospective comparison of biopsy results from curettage and hysteroscopy in postmenopausal uterine bleeding. J Obstet Gynaecol Res 2011;37:1423-6.
26. Bettocchi S, Nappi L, Ceci O, Santoro A, Fattizzi N, Nardelli C, et al. The role of office hysteroscopy in menopause. J Am Assoc Gynecol Laparosc 2004;11:103-6.
27. Spicer JM, Siebert I, Kruger TF. Postmenopausal bleeding: a diagnostic approach for both private and public sectors. Gynecol Obstet Invest 2006;61:174-8.
28. de Wit AC, Vleugels MP, de Kruif JH. Diagnostic hysteroscopy: a valuable diagnostic tool in the diagnosis of structural intra-cavital pathology and endometrial hyperplasia or carcinoma?. Six years of experience with non-clinical diagnostic hysteroscopy. Eur J Obstet Gynecol Reprod Biol 2003;110:79-82.
29. Butureanu SA, Socolov RM, Pricop F, Gafitanu DM. Diagnostic hysteroscopy in endometrial hyperplasia. Gynecol Obstet Invest 2005;59:59-61.
30. Angioni S, Loddo A, Milano F, Piras B, Minerba L, Melis GB. Detection of benign intracavitary lesions in postmenopausal women with abnormal uterine bleeding: a prospective comparative study on outpatient hysteroscopy and blind biopsy. J Minim Invasive Gynecol 2008;15:87-91.
31. Garuti G, Sambruni I, Colonnelli M, Luerti M. Accuracy of hysteroscopy in predicting histopathology of endometrium in 1500 women. J Am Assoc Gynecol Laparosc 2001;8:207-13.
32. Gambacciani M, Monteleone P, Ciaponi M, Sacco A, Genazzani AR. Clinical usefulness of endometrial screening by ultrasound in asymptomatic postmenopausal women. Maturitas 2004;48:421-4.
33. Breijer MC, Peeters JA, Opmeer BC, Clark TJ, Verheijen RH, Mol BW, et al. Capacity of endometrial thickness measurement to diagnose endometrial carcinoma in asymptomatic postmenopausal women: a systematic review and meta-analysis. Ultrasound Obstet Gynecol 2012;40:621-9.
34. Smith-Bindman R, Weiss E, Feldstein V. How thick is too thick? When endometrial thickness should prompt biopsy in postmenopausal women without vaginal bleeding. Ultrasound Obstet Gynecol 2004;24:558-65.
35. Giannella L, Mfuta K, Setti T, Boselli F, Bergamini E, Cerami LB. Diagnostic accuracy of endometrial thickness for the detection of intra-uterine pathologies and appropriateness of performed hysteroscopies among asymptomatic postmenopausal women. Eur J Obstet Gynecol Reprod Biol 2014;177:29-33.
36. Genc M, Genc B, Sahin N, Celik E, Turan GA, Gur EB, et al. Endometrial pathology in postmenopausal women with no bleeding. Climacteric 2015;18:241-5.
37. de Godoy Borges PC, Dias R, Bonassi Machado R, Borges JB, Spadoto Dias D. Transvaginal ultrasonography and hysteroscopy as predictors of endometrial polyps in postmenopause. Womens Health (Lond) 2015;11:29-33.
38. Gambacciani M, Monteleone P, Ciaponi M, Sacco A, Genazzani AR. Clinical usefulness of endometrial screening by ultrasound in asymptomatic postmenopausal women. Maturitas 2004;48:421-4.

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Effects of the morbid obesity and skin incision choices on surgical outcomes in patients undergoing total abdominal hysterectomy

Morbid obezite ve deri insizyon seçiminin total abdominal histerektomi uygulanan hastaların cerrahi sonuçlarına etkisi

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Abstract

Objective: This study aimed to evaluate the effect of obesity on surgical outcomes in patients who underwent gynecologic surgery.

Materials and Methods: In total, we evaluated 132 patients who underwent total abdominal hysterectomy with or without salpingo-oophorectomy for benign gynecologic procedures at our tertiary referral gynaecology clinic.

Results: The non-morbid obese group [body mass index (BMI) <40 kg/m^2] included 94 patients, and the morbid obese group (BMI ≥40 kg/m^2) included 38 patients. The perioperative outcomes of the groups were compared. The mean operative time was significantly longer for morbid obese patients than non-morbid obese patients ($p<0.05$). Estimated blood loss, the need for blood transfusion, postoperative hemoglobin values, and the need for an intraabdominal drain were similar between the groups. Early and late postoperative complications were significantly more frequent in the morbid obese group than the other group ($p<0.05$, for each). Early postoperative complications in patients who underwent vertical skin incision were significantly more frequent than in patients who underwent pfannenstiel incision ($p<0.05$). Late complications were comparable between the two types of skin incision.

Conclusion: Morbid obesity significantly increases the mean operative times and the postoperative complication rates of abdominal hysterectomy operations.

Keywords: Morbid obesity, gynecologic surgery, complications, wound infection, hysterectomy

Öz

Amaç: Bu çalışma jinekolojik cerrahi geçiren hastalarda, obezitenin cerrahi sonuçlara etkisini değerlendirmeyi amaçladı.

Gereç ve Yöntemler: Tersiyer referans merkezimizin jinekoloji kliniğinde, beraberinde salpingooforektomi yapılan ya da yapılmayan total abdominal histerektomi uygulanmış toplam 132 hastayı değerlendirdik.

Bulgular: Morbid obez olmayan grup [vücut kitle indeksi (VKİ) <40 kg/m^2] 94 hasta ve morbid obez grup (VKİ ≥40 kg/m^2) 38 hastadan oluşturuldu. Grupların perioperatif sonuçları karşılaştırıldı. Morbid obez hastaların ortalama operasyon süresi önemli ölçüde daha uzundu ($p<0,05$). Tahmini kan kaybı, kan transfüzyon ihtiyacı, postoperatif hemoglobin düzeyleri ve batın içi dren ihtiyacı gruplar arasında benzerdi. Erken ve geç postoperatif komplikasyonlar morbid obez grupta diğer gruptan önemli derecede daha sıktı ($p<0,05$, her biri için). Erken postoperatif komplikasyonlar, vertikal deri kesisi uygulanan hastalarda pfannenstiel kesi uygulanan hastalara göre önemli ölçüde daha sıktı ($p<0,05$). Geç komplikasyonlar iki tip deri insizyonu arasında benzer orandaydı.

Sonuç: Morbid obezite, abdominal histerektomi operasyonlarında ortalama operasyon süresi ve postoperatif komplikasyon oranlarını önemli ölçüde arttırmaktadır.

Anahtar Kelimeler: Morbid obezite, jinekolojik cerrahi, komplikasyonlar, yara enfeksiyonu, histerektomi

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Introduction

Obesity is a common health problem and is defined as a body mass index (BMI) of 30 kg/m^2 or greater; morbid obesity is defined as a BMI ≥40 kg/m^2[1]. In the United States of America, the incidence of obesity among adults has been reported to increase two-fold during the past decade[2]. In European and Mediterranean regions, the incidence of overweight (i.e., BMI between 25 and 30 kg/m^2) and obesity have increased during recent decades, regardless of the level of development[3-5].

Obesity is associated with an increased risk of diabetes mellitus, polycystic ovary syndrome, hypertension, dyslipidaemia and coronary heart diseases[6]. Obese patients have a significantly higher risk of postoperative myocardial infarction, surgical site infections, nerve injury, and urinary infection. Obesity is an independent risk factor for perioperative morbidity, and morbid obesity is a risk factor for perioperative mortality[7,8].

Laparotomy is frequently used in surgical procedures for gynecologic disorders, such as myomas, adnexal masses, and tubo-ovarian abscess[9]. Due to the increasing weight of the population, we encounter more obese patients in our gynecologic practice, even if we try to keep them away from surgical interventions. Physicians should avoid surgery (especially open abdominal surgery) in obese and morbid obese patients as well as they can. In laparotomies for gynecologic diseases, we generally use two types of skin incision. Pfannenstiel incisions are preferred because this type of incision provides adequate vision in the pelvic area and has good cosmetic results. However, a vertical skin incision is sometimes preferred for a giant myoma or a giant adnexal mass[10].

There are insufficient data in the literature regarding complication rates arising from morbid obesity and the chosen type of skin incision in benign gynecologic hysterectomies. Thus, we aimed to evaluate the effect of morbid obesity and the type of incision on complication rates among patients who underwent surgery in our clinic.

Materials and Methods

This retrospective study was performed between June 2006 and February 2007 at Etlik Zübeyde Hanım Women's Health Training and Research Hospital, which is a tertiary referral center in Ankara. Ethical approval for our study was obtained from the Local Ethics Committee. The research was completed in accordance with the Helsinki Declaration[11]. It included adult women who attended to our hospital for a benign gynecologic pathology and underwent total abdominal hysterectomy. Patients were excluded if they had any malignant disease, skin disease (such as psoriasis), autoimmune disease or were immunosuppressed. All patients were Caucasian Turkish women with no history of alcohol or drug use before and after surgery. We collected data from hospital records and patient files, and the same author called all patients to inquire about the presence of any complications within 30 days of surgery or more lately after discharge from the hospital. The subject characteristics and demographics were analyzed. Demographic preexisting variables included age, BMI, obstetric history, tobacco use, history of any previous abdominal surgery, and presence of any systemic comorbidity. BMI (kilograms per square meter) was calculated using the patient's height and weight. The subjects were divided into two BMI categories according to the World Health Organization classification system[12]. The morbid obesity group included consecutive subjects who had a BMI ≥40 kg/m^2, and the non-morbid obesity group included consecutive subjects who had a BMI lower than 40 kg/m^2.

Moreover, we classified the same samples into sub-groups in terms of skin incision types: vertical incision or pfannenstiel incision. All surgeries were performed by the same surgical team using a standardized technique. We performed surgery for benign gynecologic disorders such as myoma uteri, adnexal mass, persistent uterine hemorrhage, and tubo-ovarian abscess, and performed total abdominal hysterectomies with or without salpingo-oophorectomy for all subjects, based on the indication for surgery. Operative time (minutes), preoperative and postoperative haemoglobin (Hb) values (g/dL), estimated blood loss (EBL) (mL), requirement for blood product transfusion, length of hospital stay (days), and drain presence were recorded for each patient. A surgical drain was placed into the abdominal space based on the preference of the surgeon. When the thickness of the subcutaneous layer was greater than 2 centimetres, the subcutaneous space was closed with 2/0 poliglactic acid-poliglactin (vicryl). Subcutaneous drains were not used in any case. Cefazolin (1 gram) was used as the primary preoperative prophylaxis; clindamycin was used for patients with a history of penicillin allergy. Both drugs were administered intravenously, and additional doses were administered when the operation lasted longer than two hours. Prophylaxis for venous thromboembolic events was performed according to the chest guidelines released by the American College of Chest Physicians[13]. Early postoperative complications were defined as complications that occurred during the operation or within 30 days of the surgery. Late postoperative complications were defined as complications that occurred more than 30 days after the surgery. The operative time was defined as the time from the first skin incision to the final closure of the skin incision. Wound complications were defined as a subcutaneous infection or hemorrhage requiring surgical debridement and repair. Superficial skin separation was not considered as a wound complication. Wound infection was defined as a wound with purulent or serous drainage in combination with tissue warmth, erythema, and increasing tenderness. The primary outcome measure was defined as the presence of any early and/or late complications in morbid obese patients. The presence of complications with any incision type was also recorded. Continuous variables were recorded as the mean ± standard deviation or the median and interquartile ranges, and categorical variables were reported as frequencies and column percentages. The normality of the variables was analyzed using the Kolmogorov-Smirnov test. Student's t-test

was used to compare normally distributed continuous variables, and the Mann-Whitney U test was used to compare non-normally distributed continuous variables. The chi-square test or Fisher's exact test (when chi-square test assumptions do not hold due to low expected cell counts), where appropriate, was used to compare categorical variables. Two-sided p-values were considered statistically significant at $p<0.05$. Statistical analyses were performed using the statistical package SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

The demographic characteristics of a total of 132 patients are listed in Table 1. Patients in the study group with morbid obesity were significantly older and had a significantly higher prevalence of comorbidities than patients in the non-morbid obesity group. The two groups were similar with respect to tobacco use, previous abdominal surgery, and menopause status.

Perioperative outcomes

The surgical data of the two groups are shown in Table 2. Skin incision types were comparable between the two groups. Vertical incisions were midline incisions below the umbilicus in all cases except one, in which the incision also extended above the umbilicus. The pre-operative Hb values were significantly lower, and the mean operative time (minutes) was significantly longer in the morbid obesity group than the non-morbid obesity group. EBL, the requirement for blood transfusion, post-operative Hb values, and the presence of an abdominal drain were similar between groups. The mean length of hospital stay was longer in the group with morbid obesity than the other group (Table 2).

Complications

In our study, no intraoperative complications were observed, but there were some post-operative complications. We assessed the effect of morbid obesity on post-operative complications (Table 3). Early and late complications were significantly more frequent in the morbid obesity group than the non-morbid obesity group. We observed no wound cellulitis or fascial dehiscence in any patients.

We also compared the complications between incision types (i.e., vertical and pfannenstiel). Patients with a vertical incision had significantly more early complications (n=9; 23.1%) than patients with a pfannenstiel incision (n=3; 3.2%) ($p<0.05$). Late complications occurred in 4 subjects (10.3%) in the vertical incision group and 3 subjects (3.2%) in the pfannenstiel incision group. No significant differences in late complications were observed between the two types of skin incision (Table 4).

Discussion

We assessed the consequences of morbid obesity in our gynecologic surgery practice. Morbidly obese patients had more comorbidities, longer operation times, longer hospital stays, more early and late complications than the other group

Table 1. Individual characteristics of the patients in the two groups

	Morbid obesity (BMI ≥40 kg/m²) (n=38, 28.8%)	Non-morbid obesity (BMI <40 kg/m²) (n=94, 71.2%)	p value
Age (years)	45.52±5.66	42.23±6.41	<0.05*
Number of living children >3	11 (28.9%)	8 (8.5%)	<0.05^{w}
Tobacco use	3 (7.9%)	15 (16%)	NS^{w}
Preoperative body mass index (kg/m²)	42.62±2.71	28.32±5.00	<0.05*
Previous abdominal surgery	11 (28.9%)	22 (23.4%)	NS^{w}
Comorbidities	12 (31.57%)	14 (14.89%)	<0.05$^{P\chi}$
Hypertension	5 (13.15%)	4 (4.25%)	<0.05$^{P\chi}$
Diabetes mellitus	1 (2.63%)	8 (8.51%)	<0.05$^{P\chi}$
Thyroid dysfunction	1 (2.63%)	0	<0.05$^{P\chi}$
Heart disease	4 (10.52%)	4 (4.25%)	<0.05$^{P\chi}$
COLD	0	1 (1.06%)	<0.05$^{P\chi}$
Epilepsy	0	1 (1.06%)	<0.05$^{P\chi}$
SLE	3 (7.89%)	5 (5.31%)	NS$^{P\chi}$
Menopause	11 (28.9%)	22 (23.4%)	NS^{w}

*Independent samples t-test (values are given as mean ± standard deviation), ^{w}: Fisher's exact test (values are given as number and percentage in brackets), $^{P\chi}$: Pearson's chi-square (values are given as number and percentage in brackets), NS: Not-significant, COLD: Chronic obstructive lung disease, SLE: Systemic lupus erythematosus, BMI: Body mass index

of patients. History of previous abdominal surgery, tobacco use, menopause status, and skin incision types were comparable between the two groups, so these variables are not likely to affect differential complication rates. Hysterectomy is the most common major gynecologic surgery[14]. To our knowledge, no recent study in the literature has evaluated complications related to obesity and chosen skin incision types in benign gynecologic practice. Some studies investigated obesity and gynecologic cancer surgery[15,16]. However, benign gynecologic operations are performed more frequently than gynecologic cancer operations. The pelvic area where we performed surgery was deeper in morbidly obese patients, and the surgeons had difficulty obtaining an adequate field of vision; thus, a longer operative time was needed in morbidly obese patients. A study by Kodama et al.[16] demonstrated that a longer operative time was an independent predictor of the incidence of early

Table 2. Perioperative characteristics of the two groups

Characteristics	Morbid obesity (n=38, 28.8%)	Non-morbid obesity (n=94, 71.2%)	p value
Pfannenstiel incision	22 (57.9%)	71 (75.5%)	NS^{w}
Vertical incision	16 (42.1%)	23 (24.5%)	NS^{w}
Indications for hysterectomy	-	-	
Myoma uteri	26 (68.4%)	84 (89.4%)	
Adnexal mass	10 (26.3%)	8 (8.5%)	<0.05$^{P\chi}$
Persistent uterine hemorrhage	1 (2.6%)	2 (2.1%)	
Tubo-ovarian abscess	1 (2.6%)	0	
Salpingo-oophorectomy	-	-	
Not performed	21 (55.3%)	79 (84%)	<0.05$^{P\chi}$
Unilateral	6 (15.8%)	5 (5.3%)	
Bilateral	11 (28.9%)	10 (10.6%)	
Preoperative Hb (g/dL)	10.63±2.49	11.58±2.06	<0.05*
Postoperative Hb (g/dL)	10.05±1.61	10.53±1.83	NS*
Operative time (minute)	90.78±28.79	80.58±23.28	<0.05*
Estimated blood loss (mL)	150 (100)	175 (250)	NS
Need for blood transfusion	6 (15.8%)	6 (6.4%)	NS^{w}
Length of hospital stay (days)	3 (2)	2 (1)	<0.05†
Need for intraabdominal drain	6 (15.78%)	9 (9.57%)	NS^{w}

*Independent samples t-test (values are given as mean ± standard deviation), $^{P\chi}$: Pearson chi-square (values are given as number and percentage in brackets),^{w}: Fisher's exact test (values are given as number and percentage in brackets), †: Mann-Whitney U test (values are given as median and interquartile range in brackets), NS: Not-significant, Hb: Hemoglobin

Table 3. Comparison of post-operative complications between groups

	Morbid obesity (n=38, 28.8%)	Non-morbid obesity (n=94, 71.2%)	p value
Early complications	8 (21.1%)	4 (4.3%)	<0.05$^{P\chi}$
Wound infection	6	0	
Arrhythmia	1	0	
Hematoma	0	2	
Lung oedema	0	1	
Ileus	1	1	
Late complications	5 (13.2%)	2 (2.1%)	<0.05^{w}
Ileus	4	1	
Incisional hernia	1	1	

$^{P\chi}$: Pearson's chi-square (values are given as number and percentage in brackets), ^{w}: Fisher's exact test (values are given as number and percentage in brackets)

postoperative complications. The results of our study confirmed this finding.

A previous study stated that obese women had greater blood loss, longer operative times and hospital stays, and an increased rate of wound infection in comparison to non-obese patients[17]. However, we obtained different results concerning blood loss, because we observed no differences in EBL, postoperative Hb or the need for blood transfusion between the two groups. In our daily practice, we attempt to mobilize morbidly obese patients as early as possible, direct them to use antiembolic stockings to prevent thromboembolic events, and encourage them to return to their daily lives. The utmost importance of thromboembolic prophylaxis in morbid obese patients was denoted well in a systematic review by Hodges et al.[18]. Increased venous stasis, which has already been provoked by morbid obesity and major surgery, has been cited as responsible for venous thromboembolism[13]. In our study, no intraoperative complications were detected. We can attribute it to our experienced surgical team. A recent study performed by the Gynecologic Oncology Group LAP2 reported no differences in intra-operative complications between obese and non-obese patients[19]. Another study found that obese patients did not experience an increased risk of serious morbidity after vaginal and abdominal hysterectomy compared with normal weight women[20]. These studies compared obese and non-obese patients; however, we studied surgical complications in morbidly obese and non-morbidly obese patients. When we evaluated the groups with respect to postoperative complications, significantly higher rates of early and late complications were observed in the morbidly obese group. This finding was not surprising. In most studies, morbidly obese patients have been found to have a greater risk of postoperative complications than non-obese patients[21]. A study about vaginal procedures in overweight patients found no difference in postoperative complications between the study and the control groups[22]. However, the sample specifications and surgical procedures in that study were different from ours. In a study by Geppert et al.[23] robotic-assisted laparoscopy and open surgery for benign hysterectomy indications in obese and morbidly obese patients were compared in terms of surgical outcomes. As a result, the complication rate in the robotic surgery group was found lower than the open surgery group. However, no control groups to date have comprised normal BMI or overweight (25 kg/m^2< BMI <30 kg/m^2) patients. Therefore, that study could not have indicated the disadvantages of obesity on surgical outcomes[23]. Clinical surveys of other surgical fields, such as orthopedics and gastroenterologic surgery concluded that surgery was safe for obese patients, except in emergency operations[24,25]. Our study demonstrated that one-third of 38 patients with morbid obesity (13 patients) had one early or late complication. Most of the early complications were wound infections. In a recent study, increasing BMI was found associated with increased operative time and surgical site infections in patients undergoing abdominal hysterectomy. The results of that study are consistent with ours, but our study has different characteristics of indications for hysterectomy and salpingo-oophorectomy status[26]. We wondered whether fewer wound infections would occur if we used a subcutaneous drain. A previous study reported that subcutaneous drains and prophylactic antibiotics were recommended to minimise wound disruption[27]. However, when we reviewed the literature, we found that for patients with more than 3 cm of subcutaneous fat, the use of a subcutaneous drain was not effective for the prevention of superficial wound disruption[9]. We do not believe that surgical drains would lead to fewer wound infections because the development of a surgical site infection after a surgical procedure depends on the interaction between the host, the microorganism, and the surgical environment. In our study, no significant differences were observed between the non-morbidly obese and morbidly obese groups in terms of skin incision type. We investigated the complication rates according to the type of skin incision. The frequency of late complications was comparable between the two types of skin incision, but the early complication rate was significantly higher in the vertical incision group. A previous study of cesarean section revealed a higher incidence of wound complications in morbidly obese patients, and indicated that a vertical skin incision was associated with a higher rate of wound complications than a transverse incision[28]. Likewise, two other studies showed that in comparison to low transverse incisions, vertical skin incisions were associated with increases in postoperative pain, postoperative atelectasis, superficial wounds, and fascial dehiscence[10,29].

No patients in our study had major complications such as massive bleeding or bowel injuries; this finding may be have

Table 4. Comparison of early and late complications according to incision type

	Vertical incision (n=39)	Pfannenstiel incision (n=93)	p value
Early complications	9 (23.1%)	3 (3.2%)	<0.05$^{P\chi}$
Wound infection	5	1	
Arrhythmia	1	0	
Hematoma	1	1	
Ileus	2	0	
Lung edema	0	1	
Late complications	4 (10.3%)	3 (3.2%)	NS^{w}
Ileus	3	2	
Incisional hernia	1	1	

$^{P\chi}$: Pearson's chi-square (values are given as number and percentage in brackets), ^{w}: Fisher's exact test (values are given as number and percentage in brackets), NS: Not significant

been caused by the limited number of patients in the study. Further studies with a larger sample sizes may generate different findings. In our study, gynecologic operations were performed using an abdominal incision only; we did not include any vaginal or laparoscopic gynecologic surgeries. There are some limitations to our study. Absence of sample size analysis is one of them. Owing to the cross-sectional study design, all of the consecutive patients who attended our hospital and fulfilled the inclusion criteria between the mentioned dates were recruited for the study. The strengths of our study include the investigation of the effects of morbid obesity and skin incision types on surgical outcomes in major gynecologic surgery.

Conclusion

Hysterectomy with or without salpingo-oophorectomy is significantly associated with early and late postoperative complications in morbidly obese patients. Early complications in patients undergoing abdominal hysterectomy with a vertical incision were encountered more frequently than in patients undergoing hysterectomy with a transverse incision. Wound infection was seen as an early complication in predominantly morbidly obese patients. Further studies that compare larger samples with more clinical risks and complications may generate different results. Obesity remains an important factor in everyday gynecologic practice.

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Ethics

Ethics Committee Approval: The study was approved by the Etlik Zubeyde Hanim Women's Health Training and Research Hospital local ethics committee, Informed Consent: Consent form was filled out by all participants.
Peer-review: Externally and Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Özlem Evliyaoğlu, Okyar Erol, Mehmet Akif Akgül, Concept: Ebru Ersoy, Özlem Evliyaoğlu, Ali Haberal, Design: Ebru Ersoy, Okyar Erol, Ali Haberal, Mehmet Akif Akgül, Data Collection or Processing: Okyar Erol, Mehmet Akif Akgül, Analysis or Interpretation: Özlem Evliyaoğlu, Ali Özgür Ersoy, Literature Search: Ebru Ersoy, Ali Özgur Ersoy, Writing: Ebru Ersoy, Özlem Evliyaoğlu.
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References

1. Consultation WHOE. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157-63.
2. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. JAMA 2006;295:1549-55.
3. Hardy R, Wadsworth M, Kuh D. The influence of childhood weight and socioeconomic status on change in adult body mass index in a British national birth cohort. Int J Obes Relat Metab Disord 2000;24:725-34.
4. Liese AD, Doring A, Hense HW, Keil U. Five year changes in waist circumference, body mass index and obesity in Augsburg, Germany. Eur J Nutr 2001;40:282-8.
5. Sibai AM, Hwalla N, Adra N, Rahal B. Prevalence and covariates of obesity in Lebanon: findings from the first epidemiological study. Obes Res 2003;11:1353-61.
6. Health implications of obesity. National Institutes of Health Consensus Development Conference Statement. Natl Inst Health Consens Dev Conf Consens Statement 1985;5:1-7.
7. Bamgbade OA, Rutter TW, Nafiu OO, Dorje P. Postoperative complications in obese and nonobese patients. World J Surg 2007;31:556-60.
8. Giles KA, Hamdan AD, Pomposelli FB, Wyers MC, Siracuse JJ, Schermerhorn ML. Body mass index: surgical site infections and mortality after lower extremity bypass from the National Surgical Quality Improvement Program 2005-2007. Ann Vasc Surg 2010;24:48-56.
9. Guvenal T, Duran B, Demirkoprulu N, Cetin M. Prevention of superficial wound disruption in Pfannenstiel incisions by using a subcutaneous drain. Int J Gynaecol Obstet 2002;77:151-3.
10. Alanis MC, Villers MS, Law TL, Steadman EM, Robinson CJ. Complications of cesarean delivery in the massively obese parturient. Am J Obstet Gynecol 2010;203:271.
11. World Medical A. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310:2191-4.
12. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser 2000;894:1-253.
13. Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:338-400.
14. Whiteman MK, Hillis SD, Jamieson DJ, Morrow B, Podgornik MN, Brett KM, et al. Inpatient hysterectomy surveillance in the United States, 2000-2004. Am J Obstet Gynecol 2008;198:1-7.
15. Everett E, Tamimi H, Greer B, Swisher E, Paley P, Mandel L, et al. The effect of body mass index on clinical/pathologic features, surgical morbidity, and outcome in patients with endometrial cancer. Gynecol Oncol 2003;90:150-7.
16. Kodama J, Seki N, Ojima Y, Nakamura K, Hongo A, Hiramatsu Y. Risk factors for early and late postoperative complications of patients with endometrial cancer. Eur J Obstet Gynecol Reprod Biol 2006;124:222-6.
17. Pitkin RM. Abdominal hysterectomy in obese women. Surg Gynecol Obstet 1976;142:532-36.
18. Hodges KR, Davis BR, Swaim LS. Prevention and management of hysterectomy complications. Clin Obstet Gynecol 2014;57:43-57.
19. Gunderson CC, Java J, Moore KN, Walker JL. The impact of obesity on surgical staging, complications, and survival with uterine cancer: a Gynecologic Oncology Group LAP2 ancillary data study. Gynecol Oncol 2014;133:23-7.
20. Rasmussen KL, Neumann G, Ljungstrom B, Hansen V, Lauszus FF. The influence of body mass index on the prevalence of complications after vaginal and abdominal hysterectomy. Acta Obstet Gynecol Scand 2004;83:85-8.

21. Stamilio DM, Scifres CM. Extreme obesity and postcesarean maternal complications. Obstet Gynecol 2014;124:227-32.
22. Tuschy B, Berlit S, Kehl S, Sutterlin M, Bussen S. Influence of overweight in elderly patients undergoing vaginal surgery due to pelvic floor disorders. In Vivo 2012;26:1069-73.
23. Geppert B, Lonnerfors C, Persson J. Robot-assisted laparoscopic hysterectomy in obese and morbidly obese women: surgical technique and comparison with open surgery. Acta Obstet Gynecol Scand 2011;90:1210-7.
24. Vignali A, De Nardi P, Ghirardelli L, Di Palo S, Staudacher C. Short and long-term outcomes of laparoscopic colectomy in obese patients. World J Gastroenterol 2013;19:7405-11.
25. Buerba RA, Fu MC, Gruskay JA, Long WD, Grauer JN. Obese Class III patients at significantly greater risk of multiple complications after lumbar surgery: an analysis of 10,387 patients in the ACS NSQIP database. Spine J 2014;14:2008-18.
26. Mikhail E, Miladinovic B, Velanovich V, Finan MA, Hart S, Imudia AN. Association between obesity and the trends of routes of hysterectomy performed for benign indications. Obstet Gynecol 2015;125:912-8.
27. Gallup DC, Gallup DG, Nolan TE, Smith RP, Messing MF, Kline KL. Use of a subcutaneous closed drainage system and antibiotics in obese gynecologic patients. Am J Obstet Gynecol 1996;175:358-61.
28. Wall PD, Deucy EE, Glantz JC, Pressman EK. Vertical skin incisions and wound complications in the obese parturient. Obstet Gynecol 2003;102:952-6.
29. Bell J, Bell S, Vahratian A, Awonuga AO. Abdominal surgical incisions and perioperative morbidity among morbidly obese women undergoing cesarean delivery. Eur J Obstet Gynecol Reprod Biol 2011;154:16-9.

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The impact of abdominal and laparoscopic hysterectomies on women's sexuality and psychological condition

Abdominal ve laparoskopik histerektomilerin kadın cinselliği ve psikolojik durumuna etkileri

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Abstract

Objective: To investigate whether there were any differences in the quality of life, sexual function, and self-esteem of patients who underwent total laparoscopic hysterectomy (TLH) (n=42) and total abdominal hysterectomy (TAH) (n=42).

Materials and Methods: All premenopausal patients who underwent TLH or TAH because of benign uterine disorders were enrolled. The sexual function and quality of life status were assessed preoperatively and 6 months postoperatively using three standardized validated questionnaires: the Arizona Sexual Experiences Scale (ASEX), the Symptom Checklist-90-Revised (SCL-90-R), and the Rosenberg Self-Esteem Scale (RSES).

Results: Preoperative ASEX, SCL-90-R and RSES scores were not different among the hysterectomy subgroups. The postoperative SCL-90-R scores were also not different among the hysterectomy subgroups. The postoperative RSES scores were significantly lower ($p<0.05$) than the preoperative scores for all procedures (indicating improved self-esteem) but did not differ among the groups. The postoperative ASEX scores were significantly decreased ($p<0.01$) as compared with the preoperative scores (indicating improved sexual function). When the average score of each item of the ASEX score was compared in both groups, significant differences were observed in sexual drive and arousal in the laparoscopy group ($p<0.01$).

Conclusion: Women undergoing TLH for benign uterine disease may have better outcomes related to certain sexual function parameters than women undergoing TAH.

Keywords: Total abdominal hysterectomy, total laparoscopic hysterectomy, sexual function, self-esteem, quality of life

Öz

Amaç: Benign nedenler ile total laparoskopik histerektomi (TLH) veya total abdominal histerektomi (TAH) operasyonu olan hastalarda ameliyat şeklinin hastanın yaşam kalitesi, cinsel işlev ve benlik saygısına olan etkisini araştırmayı amaçladık.

Gereç ve Yöntemler: Benign uterin hastalık endikasyonuyla TLH (n=42) veya TAH (n=42) yapılan premenopozal cinsel olarak aktif hastalar çalışmaya dahil edildi. Cinsel fonksiyon ve yaşam kalitesi preoperatif ve postoperatif 6. ay da standardize ve valide edilmiş anketler ile değerlendirildi.

Cinsel fonksiyonlar Arizona Cinsel Yaşam Skalası (ASEX) ile Revize Edilmiş Psikolojik Belirti Taraması-90 (SCL-90-R) formu ile benlik saygısı ise Rosenberg Benlik Saygı Ölçeği Skalası (RSES) kullanılarak değerlendirildi.

Bulgular: Preoperatif ASEX, SCL-90-R ve RSES skorlarında histerektomi grupları arasında fark izlenmedi ($p>0,05$). Postoperatif 6. ayda bakılan SCL-90-R puanları da histerektomi alt grupları arasında farklı değildi ($p>0,05$). Postoperatif RSES puanları tüm prosedürler için preoperatif puanlardan anlamlı olarak daha düşük bulundu (benlik saygısında artma) ($p<0,05$), ancak gruplar arasında anlamlı farklılık izlenmedi ($p>0,05$).

Postoperatif 6. ayda bakılan ASEX puanları preoperatif puanları ile karşılaştırıldığında anlamlı derecede azalmıştır ($p<0,01$) (cinsel fonksiyonlarda iyileşme). Her iki grubun ASEX alt grup skorları karşılaştırıldığında laparoskopi grubunda cinsel dürtü ve uyarılma skorlarında anlamlı farklılık gözlenmiştir ($p<0,01$).

Sonuç: Benign endikasyonla TLH olan kadınların TAH olan kadınlara göre daha iyi cinsel fonksiyon sonuçları gösterebilir.

Anahtar Kelimeler: Total abdominal histerektomi, total laparoskopik histerektomi, cinsel fonksiyon, benlik saygısı, yaşam kalitesi

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Introduction

Hysterectomy is one of the most common gynecologic operations performed in developed countries and is usually performed for benign disorders[1,2].

Sexual function and the quality of life have been the focus of many recent studies. Investigation of the effects of hysterectomy performed for benign indications on sexual function and postoperative quality of life have led to varied results. Hysterectomy may cause sexual dysfunction in the postoperative period[3,4]. On the other hand, abnormal uterine bleeding, endometriosis, and adnexal or uterine pathologies can lead to sexual problems, and pain reduce quality of life[5]. The rapid progress made in laparoscopic surgery over the past 20 years has been a crucial development in gynecologic surgery and plays a role in the determination of treatment[6]. The most significant benefits of laparoscopic surgery include decreased blood loss, lower risk of surgical site infections, shorter hospital stays, and rapid return to normal daily activities in laparoscopy compared with laparotomy[7]. However, studies investigating postoperative psychological effects and effects on sexual function are limited.

In the present study, we conducted a prospective cohort trial investigating the advantages and potential drawbacks regarding the sexual function of patients who underwent laparoscopic and abdominal hysterectomy. Our goal was to investigate whether there were any differences in the quality of sexual function postoperatively.

Materials and Methods

The present prospective cohort study was conducted in Zeynep Kamil Training and Research Hospital, which is one of the largest tertiary teaching hospitals in Turkey. All patients provided informed consent. Approval from the local ethics committee was acquired. Preoperatively, all patients underwent gynecologic examination, transvaginal ultrasounds, medical histories were obtained, and routine laboratory tests were performed.

Patients for whom hysterectomy without concurrent unilateral or bilateral adnexectomy was indicated for a benign gynecologic condition, who had a stable heterosexual relationship for at least 1 year, and who had no psychiatric disorders were included in the study. The exclusion criteria were suspicion of malignancy, a previous lower midline incision, the need for simultaneous interventions such as prolapse repair, the need for intraoperatively diagnosed adnexal pathology requiring subsequent unilateral or bilateral oophorectomy, having preoperative or postoperative hormone-therapy, and an inability to communicate in Turkish. In addition, patients with psychiatric disorders, vaginismus, lack of orgasm, a history of endometriosis, partners with sexual dysfunction, those who refused the interview, lost to follow-up, loss of sexual interest, psychological and physiological problems with partner's relationship, and in postmenopausal period were excluded from the study. The patients and their physician had decided to the route of hysterectomy. The patients were included in the study if they were scheduled for abdominal or laparoscopic hysterectomy. Patients were divided into two groups according to the surgical treatment: the total abdominal hysterectomy (TAH) group and the total laparoscopic hysterectomy (TLH) group. The demographic characteristics (age, marital status, education, and occupation) were recorded. The sexual function and quality of life were assessed 1 day preoperatively on admission to our hospital. Both of the groups' patients were contacted 6 months postoperatively and interviewed again. All questionnaires were coded with an identifying number, and women could not view their previous answers. We confirmed that all of the patients had had sexual intercourse again six months after surgery. All data were recorded and analyzed by another researcher who was blinded to the group assignments.

Operating procedures

All patients underwent general anesthesia and received preoperative antibiotic prophylaxis as well as anticoagulants during immobilization. Laparoscopic hysterectomies were all intentionally TLHs[8] and TAH was performed using the standard extrafascial technique by means of clamps and suture ligation[9]. The technical aspects of both types of hysterectomy were discussed with each patient, and the appropriate hysterectomy type was selected through mutual discussion.

Questionnaires

Sexual dysfunction and quality of sexual life, psychological health status, and self-esteem were assessed preoperatively and 6 months postoperatively using standardized validated questionnaires: the Arizona Sexual Experiences Scale (ASEX), the Symptom Checklist-90-Revised (SCL-90-R), and the Rosenberg Self-Esteem Scale (RSES).

Arizona Sexual Experiences Scale

The patients'quality of sexual life was measured using the ASEX scale. The ASEX is a five-item scale with six different levels of answers that measure sexual function. The questionnaire enquires about sex drive, arousal, vaginal lubrication, ability to reach orgasm, and satisfaction with orgasm. The female and male versions of the ASEX differ on the sex-specific question 3, which addresses erection/lubrication. A total ASEX score of ≥19, any one item with an individual score of 5 or 6, and three or more items with individual scores of 4 have all been found highly correlated with physician-diagnosed sexual dysfunction[10]. Patients whose partners had sexual dysfunction were eliminated from the study. We used the Turkish version of the inventory, which has been proven valid and reliable by a recent study (Cronbach's alpha=0.91)[11].

Symptom Checklist-90-Revised Scale

SCL-90-R was used to evaluate the psychological health status of the patients. The SCL-90-R includes items about psychosomatic symptoms of the patient and covers nine scales:

1. Somatization;
2. Obsessive-compulsive behavior;
3. Interpersonal sensitivity;
4. Depression;
5. Anxiety;
6. Hostility;
7. Phobic anxiety;
8. Paranoid ideation;
9. Psychoticism[12,13].

Stressful personality, depression, anxiety, and somatization are generally measured using five-point scales (sores between 0-4)[14]. Increasing scores generally indicate that the patient is anxious about the symptoms and signs. We used the Turkish version of the inventory, which has been proven valid and reliable by a recent study (Cronbach's alpha=0.83)[15].

Rosenberg Self-Esteem Scale

RSES consists of 10 items for assessing levels of self-esteem. The items are answered on a four-point scale using anchors of strongly agree (0) and strongly disagree. Its reliability and validity in Turkish were confirmed in 1986 by Çuhadaroğlu[16] and the first 10 items of the test, which assess self-esteem, were used. The subjects achieve scores between 0 and 6 according to the self-assessment system of the scale. A score of 0-1 is considered high self-esteem, a score of 2-4 is considered moderate self-esteem, and a score of 5-6 is considered low self-esteem. A high score indicates low self-esteem, whereas a low score indicates high self-esteem.

Statistical Analysis

Statistical analysis was performed using SPSS version 21.0 for Windows. Values are expressed as mean ± standard deviation. The Kolmogorov-Smirnov test was performed to assess the distribution of data. A comparison of two groups was performed using Student's t-test or Mann-Whitney U test for continuous variables, and the chi-square test for categorical variables. Comparisons of preoperative and postoperative scores were performed using the paired-samples t-test and Wilcoxon test. A p value of <0.05 was considered to indicate statistical significance.

Results

The patient flow chart is listed in detail in Figure 1. Out of 150 eligible patients, 84 completed the study. The demographic and clinical data of the two groups are summarized in Table 1.

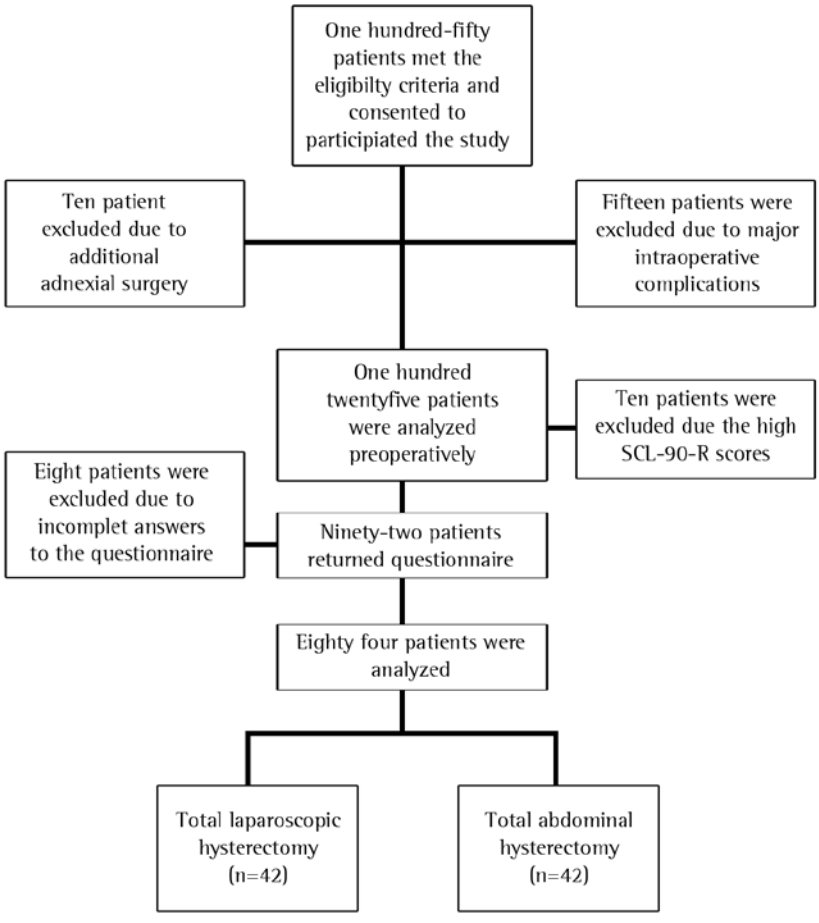

Figure 1. Flow chart of study design

SCL-90-R: Symptom Checklist-90-Revised

Table 1. Patients' sociodemographic variables and medical characteristics prior to surgery

	Group 1 (TAH) Mean ± SD % (n)	Group 2 (TLH) Mean ± SD % (n)	p
Age (year)	42.8±2.5	41.1±5.5	0.161[m]
BMI (kg/cm2)	28.6±4.0	29.5±6.9	0.542[m]
Duration of marriage (year)	23.1±4.8	24.5±9.6	0.146[t]
Partner age (year)	46.8±3.6	48.6±6.3	0.135[t]
Education status			
Primary school	41.5% (17)	36.6% (15)	
High school	36.6% (15)	36.6% (15)	0.850
University	22.0% (9)	26.8% (11)	
Occupation			
Works	26.8% (11)	29.3% (12)	0.810
House wife	73.2% (30)	70.7% (29)	
Gravida	3.4±2.0	4.2±2.7	0.146[m]
Parity	2.7±1.4	3.2±1.8	0.149[m]
Route of delivery			
Vaginal	75.6% (31)	85.4% (35)	0.850
Cesarean section	24.4% (10)	17.1% (7)	
Intermarriage			
Yes	19.5% (8)	26.8% (11)	0.432
No	80.5% (33)	73.2% (30)	
2nd degree	2.4% (1)	0.0% (0)	
3rd degree	12.2% (5)	12.2% (5)	
4th degree	4.9% (2)	14.6% (6)	
Marital status			
Single	9.8% (4)	7.3% (3)	
Married	90.2% (37)	92.7% (38)	0.690
Type of marriage			
Flirting	36.6% (15)	41.5%	0.650
Arranged	63.4% (26)	58.5%	
Indication of operation			
Abnormal uterine bleeding	36.6% (15)	43.9% (18)	
Endometrial hyperplasia	17.1% (7)	17.1% (7)	0.862
Myoma uteri	26.8% (11)	19.5% (8)	
Cervical pathology	19.5 % (8)	19.5% (8)	

[m]:Mann-Whitney U test/t test/chi-square test, *p<0.05, TLH: Total laparoscopic hysterectomy, TAH: Total abdominal hysterectomy, SD: Standard deviation

There were no statistically significant differences in the pre-and postoperative SCL-90-R scores between the groups (p>0.05) (Table 2).

Both groups exhibited a statistically significant decrease in the postoperative RSES scores compared with the preoperative scores (p<0.05). However, there were no statistically significant differences between the groups (p>0.05) (Table 3). Evaluations of sexual function are summarized in Table 4. No differences were observed between the two groups preoperatively. Postoperative decreases in ASEX scores (improvement in sexual function) were observed in both groups. Improvement in sex drive score and psychological arousal scores were better in the laparoscopic hysterectomy group compared with the abdominal group (p<0.01).

Discussion

In the present study, decreased ASEX scores were observed 6 months postoperatively in both groups. This was more remarkable in the laparoscopy group compared with the laparotomy group. Both groups showed improvement in RSES scores; however, no significant difference was observed. Regarding the psychiatric evaluation, there were no significant differences between the groups preoperatively and 6 months postoperatively. The effects of hysterectomy on women's sexuality are controversial, and sexual function in the post-hysterectomy period is a complicated and uncertain issue by means of its results[17-21]. Hysterectomy may increase the quality of life in patients who did not respond to conservative therapy by relieving symptoms[22]. Nevertheless, patients preparing for hysterectomy may experience fear and anxiety of sexual function loss[23]. Hysterectomy is a loss because the uterus is an organ to which women are connected psychologically. Psychosexual problems after hysterectomy are usually related to marital issues and poor body image, which are exacerbated with hysterectomy. Age, biologic and psychological factors, relationships and social and cultural circumstances affect a woman's sexuality[2,24]. Therefore, women's sexuality needs to be assessed through many independent factors. On the other hand, preoperative sexual function and psychological status are also important determinants of sexual dysfunction postoperatively. In our study, essential factors affecting sexuality such as self-respect and psychological status were evaluated. We observed no statistically significant changes in psychiatric scores in either group; however, amelioration of self-respect was observed postoperatively, and in our opinion, this may be a substantial factor affecting sexual improvement. In order to ensure a homogenous study population, we excluded patients with high preoperative psychiatric scores. Thus, we aimed to assess the effect of the operation on sexual life and also on the patient's psychology. Following hysterectomy, elimination of pain, discomfort, resistant menometrorrhagia associated with present disease, and risk of cancer and unwanted pregnancy may result in higher frequency of orgasms and a more satisfying sexual life[25].

Table 2. Comparison of Symptom Checklist-90-Revised preoperative and postoperative 6th month

SCL-90-R	Group 1 (TAH)	Group 2 (TLH)	*p
Somatization score			
Preoperative	1.3±1.0	1.4±0.9	0.551[m]
Postoperative	1.2±1.0	1.2±0.9	0.927[m]
Preop-postop difference	0.0±1.1	0.3±1.0	0.666[m]
Difference p	0.190[w]	0.121[w]	
Depression score			
Preoperative	1.0±0.8	1.2±1.2	0.410[m]
Postoperative	0.8±0.9	1.0±1.3	0.659[m]
Preop-postop difference	0.1±0.9	0.3±0.9	0.707[m]
Difference p	0.158[w]	0.171[w]	
Obsessive-compulsive behavior score			
Preoperative	1.0±0.8	1.2±0.8	0.483[m]
Postoperative	0.9±1.0	1.0±0.9	0.563[m]
Preop-postop difference	0.2±1.1	0.2±0.9	0.654[m]
Difference p	0.126[w]	0.89[w]	
Anxiety score			
Preoperative	0.9±0.8	0.9±0.7	0.825[m]
Postoperative	0.8±0.9	0.7±0.7	0.979[m]
Preop-postop difference	0.1±1.0	0.3±0.8	0.527[m]
Difference p	0.441[w]	0.104[w]	
Interpersonal sensitivity score			
Preoperative	1.0±0.9	1.1±1.0	0.517[m]
Postoperative	0.8±0.9	0.8±0.8	0.372[m]
Preop-postop difference	0.2±1.1	0.4±0.8	0.930[m]
Difference p	0.051[w]	0.055[w]	
Hostility score			
Preoperative	0.8±0.8	0.7±0.6	0.551[m]
Postoperative	0.7±0.9	0.7±0.8	0.927[m]
Preop-postop difference	0.0±0.9	0.1±0.8	0.666[m]
Difference p	0.508[w]	0.501[w]	
Phobic anxiety score			
Preoperative	0.5±0.6	0.6±0.7	0.947[m]
Postoperative	0.5±0.7	0.5±0.7	0.903[m]
Preop-Postop Difference	0.0±0.8	0.1±0.6	0.866[m]
Difference p	0.656[w]	0.180[w]	

Table 2 continued. Comparison of Symptom Checklist-90-Revised preoperative and postoperative 6th month

SCL-90-R	Group 1 (TAH)	Group 2 (TLH)	*p
Paranoid ideation score			
Preoperative	0.8±0.9	0.9±0.8	0.430[m]
Postoperative	0.6±0.8	0.7±0.8	0.515[m]
Preop-postop difference	0.2±1.2	0.4±0.8	0.865[m]
Difference p	0.090[w]	0.052[w]	
Psychoticism score			
Preoperative	0.6±0.6	0.5±0.6	0.637[m]
Postoperative	0.5±0.6	0.5±0.5	0.283[m]
Preop-postop difference	0.1±0.7	0.1±0.6	0.580[m]
Difference p	0.290[w]	0.352[w]	

[m]:Mann-Whitney U test, [w]:Wilcoxon test, *p<0.05, SCL-90-R: Symptom Checklist-90-Revised, TLH: Total laparoscopic hysterectomy, TAH: Total abdominal hysterectomy

Table 3. Comparison of Rosenberg Self-Esteem Scale preoperative and postoperative 6th month

Rosenberg Self-Esteem Scale	Group 1 (TAH)	Group 2 (TLH)	**p
Preoperative	2.1±1.1	2.4±1.1	0.147[m]
Postoperative	1.1±0.8	1.0±0.6	0.907[m]
Preop-postop difference	-1.0±1.1	-1.4±1.2	0.083[m]
Difference p	0.000[w]	0.000[w]	

[m]: Mann-Whitney U test, [w]: Wilcoxon test, **p<0.05, TAH: Total abdominal hysterectomy, TLH: Total laparoscopic hysterectomy

Farrell and Kieser[26] claimed in their study that improvement in quality of life and no negative effects on sexuality were observed. The most important factor they emphasized was that there were many factors influencing sexual life and that these should be assessed in unity.

Ayoubi et al.[2] compared three types of hysterectomy (vaginal, abdominal, and laparoscopic) and found no differences in the effects on orgasm, frequency of sexual intercourse and sexual desire between groups; however, poorer body image was observed less in the TLH group compared with the TAH group. Another important finding of this study was that adverse psychological effects were observed less in the laparoscopy group. The absence of abdominal scars in the laparoscopy group and less postoperative pain may explain these findings.

A study that compared 5 different hysterectomy procedures conducted by Lermann et al.[27] reported that women in the laparoscopic supracervical hysterectomy (LASH) and TLH groups had more favorable results. However, the difference between TLH and LASH groups was not statistically significant.

The study of Lermann et al.[27] was a long-term and broad study but the retrospective study design and lack of sexual evaluation before surgery were important limitations of the study. Although statistical significant differences between the groups were not encountered, the conclusion of less invasive methods had more favorableresults was compatible with our results.

Table 4. Comparison of Arizona Sexual Experiences Scale score preoperative and postoperative

Female Arizona Sexual Experiences Scale	Group 1 (TAH)	Group 2 (TLH)	+p
Sexual drive			
Preoperative	3.3±1.2	3.6±1.2	0.185[m]
Postoperative	2.7±1.0	1.7±0.8	<0.001[m]
Preop-postop difference	0.7±1.1	1.9±1.4	<0.001[m]
Difference p	0.000[w]	0.001[w]	
Arousal			
Preoperative	3.4±1.3	3.8±0.9	0.138[m]
Postoperative	2.7±1.1	2.0±0.8	0.002[m]
Preop-postop difference	0.7±1.1	1.8±1.2	<0.001[m]
Difference p	0.000[w]	0.001[w]	
Vaginal lubrication			
Preoperative	3.1±1.0	3.4±0.8	0.180[m]
Postoperative	2.5±0.8	2.3±0.9	0.258[m]
Preop-postop difference	0.1±1.0	1.0±1.1	0.051[m]
Difference p	0.000[w]	0.002[w]	
Ability to reach orgasm			
Preoperative	3.4±1.1	3.4±1.2	0.796[m]
Postoperative	2.7±1.1	2.8±1.1	0.846[m]
Preop-postop difference	0.8±1.5	0.7±1.2	0.895[m]
Difference p	0.002[w]	0.0091[w]	
Satisfaction with orgasm score			
Preoperative	2.9±1.2	3.0±1.2	0.679[m]
Postoperative	2.4±1.2	2.0±1.0	0.105[m]
Preop-postop difference	0.6±1.1	1.0±1.4	0.064[m]
Difference p	0.000[w]	0.004[w]	
Total score			
Preoperative	16.1±4.3	17.2±3.7	0.135[m]
Postoperative	12.9±3.7	10.8±2.1	0.008[m]
Preop-postop difference	3.2±3.9	6.4±3.3	<0.001[m]
Difference p	0.000[w]	0.000[w]	

[m]: Mann-Whitney U test, [w]: Wilcoxon test, +p<0.05, TAH: Total abdominal hysterectomy, TLH: Total laparoscopic hysterectomy

Gutl et al.[28] compared vaginal hysterectomy (VH) and TAH groups. The authors assessed patients 3 months and 2 years postoperatively and observed improvement on sexual function in both groups; more pain and poor self-image were observed in the TAH group, which may be associated with abdominal scar appearance. In addition, the recovery period was longer compared with the VH group. Hehenkamp et al.[29] randomly assigned patients to undergo uterine artery embolization and hysterectomy for the treatment uterine fibroids, then assessed sexual activity and body image scales in both groups. Improvement was more apparent in the uterine artery embolization group. Less invasive methods of surgery appear to have a positive impact on quality of life and patient comfort. This favorable change in self-body image and quality of life also has indirect positive repercussions on sexual life. Both TLH and TAH groups showed decreased postoperative ASEX scores. In comparison with abdominal operations, sexual drive scores and arousal scores decreased more in the TLH group, which indicated improvement in sexual function. TLH appears to have advantages for women who require total hysterectomy for benign indications, particularly with regard to sexual functions. The main strengths of our study were the prospective observational design and the patients were chosen homogeneously. However, the small number of the study group and short follow-up period (6 months postoperatively) were the main limitations of the study.

Conclusion

In conclusion, laparoscopic surgery should be performed on suitable patients considering that it is less invasive, has a shorter recovery period, and has positive effects on sexual function and quality of life. We think that further research with a prospective long-term follow-up design is necessary to identify a surgical option associated with maximum preservation of sexual function during hysterectomy procedures.

Ethics

Ethics Committee Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Approval number: 127/2013, Informed Consent: Informed consent was obtained from all individual participants included in the study. Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Meryem Kürek Eken, Ateş Karateke, Concept: Meryem Kürek Eken, Gülşah İlhan, Evrim Erbek Çelik, Design: Ateş Karateke, Meryem Kürek Eken, Evrim Erbek Çelik, Data Collection or Processing: Meryem Kürek Eken, Dilşad Herkiloğlu, Evrim Erbek Çelik, Analysis or Interpretation: Meryem Kürek Eken, Gülşah İlhan, Osman Temizkan, Literature Search: Osman Temizkan, Evrim Erbek

Çelik, Dilşad Herkiloğlu, Writing: Meryem Kürek Eken, Gülşah İlhan, Osman Temizkan.

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References

1. Wallwiener M, Taran FA, Rothmund R, Kasperkowiak A, Auwarter G, Ganz A, et al. Laparoscopic supracervical hysterectomy (LSH) versus total laparoscopic hysterectomy (TLH): an implementation study in 1,952 patients with an analysis of risk factors for conversion to laparotomy and complications, and of procedure-specific re-operations. Arch Gynecol Obstet 2013;288:1329-39.
2. Ayoubi JM, Fanchin R, Monrozies X, Imbert P, Reme JM, Pons JC. Respective consequences of abdominal, vaginal, and laparoscopic hysterectomies on women's sexuality. Eur J Obstet Gynecol Reprod Biol 2003;111:179-82.
3. Farquhar CM, Steiner CA. Hysterectomy rates in the United States 1990-1997. Obstet Gynecol 2002;99:229-34.
4. Altman D, Granath F, Cnattingius S, Falconer C. Hysterectomy and risk of stress-urinary-incontinence surgery: nationwide cohort study. Lancet 2007;370:1494-9.
5. Pauls RN. Impact of gynecological surgery on female sexual function. Int J Impot Res 2010;22:105-14.
6. Takeda A, Imoto S, Mori M, Yamada J, Nakamura H. Management of large adnexal tumors by isobaric laparoendoscopic single-site surgery with a wound retractor. Eur J Obstet Gynecol Reprod Biol 2013;166:185-9.
7. Nieboer TE, Johnson N, Lethaby A, Tavender E, Curr E, Garry R, et al. Surgical approach to hysterectomy for benign gynaecological disease. Cochrane Database Syst Rev 2009:CD003677.
8. Thiel F, Renner S, Oppelt P, al. e. Establishment of total laparoscopic hysterectomy (TLH) in a university gynecology department: Results of the first 100 operations. Geburtshilfe und Frauenheilkunde 2006;66:665-9.
9. Mueller A, Boosz A, Koch M, Jud S, Faschingbauer F, Schrauder M, et al. The Hohl instrument for optimizing total laparoscopic hysterectomy: results of more than 500 procedures in a university training center. Arch Gynecol Obstet 2012;285:123-7.
10. McGahuey CA, Delgado LP, Geleberg AJ. Assessment of sexual dysfunction using the Arizona Sexual Experience Scale (ASEX) and implications for the treatment of depression. Psychiatric Ann 1999;29:39-45.
11. Soykan A. The reliability and validity of Arizona sexual experiences scale in Turkish ESRD patients undergoing hemodialysis. Int J Impot Res 2004;16:531-4.
12. Cunha I, Brissos S, Dinis M, Mendes I, Nobre A, Passao V. Comparison between the results of the Symptom Check List- 90-R of two different populations with temporal lobe epilepsy. Epilepsy Behav 2003;4:733-9.
13. Numan N. Exploration of adverse psychological symptoms in Yemeni khat users by the Symptoms Checklist-90 (SCL-90). Addiction 2004;99:61-5.
14. Reisch T, Vijayananda S, Gekle W, Tschacher W. [A Qualitative Follow-Up Assessment two Years after Inpatient Crisis Intervention]. Psychiatr Prax 2004;31:16-22.
15. Kılınç M. Belirti Tarama Listesi (SCL-90-R) nin Geçerlilik ve Güvenirliği. Psikolojik Danışma ve Rehberlik Dergisi 1991;1:45-52.
16. Çuhadaroğlu F. Adolesanlarda benlik saygısı. Yayınlanmamış Uzmanlık Tezi, Psikiyatri Anabilim D, Ankara, 1986.
17. Morokoff PJ, Gillilland R. Stress, sexual functioning, and marital satisfaction. J Sex Res 1993;30:43-53.
18. Richards DH. A post-hysterectomy syndrome. Lancet 1974;2:983-5.
19. Kaltreider NB, Wallace A, Horowitz MJ. A field study of the stress response syndrome. Young women after hysterectomy. JAMA 1979;242:1499-503.
20. Roovers JP, van der Bom JG, van der Vaart CH, Heintz AP. Hysterectomy and sexual wellbeing: prospective observational study of vaginal hysterectomy, subtotal abdominal hysterectomy, and total abdominal hysterectomy. BMJ 2003;327:774-8.
21. Helstrom L. Sexuality after hysterectomy: a model based on quantitative and qualitative analysis of 104 women before and after subtotal hysterectomy. J Psychosom Obstet Gynaecol 1994;15:219-29.
22. Wattiez A, Cohen SB, Selvaggi L. Laparoscopic hysterectomy. Curr Opin Obstet Gynecol 2002;14:417-22.
23. Mokate T, Wright C, Mander T. Hysterectomy and sexual function. J Br Menopause Soc 2006;12:153-7.
24. Lamont J, Society of O, Gynaecologists of C. Female sexual health consensus clinical guidelines. J Obstet Gynaecol Can 2012;34:769-83.
25. Huffman JW. Sex after hysterectomy. . Med Aspects Human Sexuality 1985;19:171-9.
26. Farrell SA, Kieser K. Sexuality after hysterectomy. Obstet Gynecol 2000;95:1045-51.
27. Lermann J, Haberle L, Merk S, Henglein K, Beckmann MW, Mueller A, et al. Comparison of prevalence of hypoactive sexual desire disorder (HSDD) in women after five different hysterectomy procedures. Eur J Obstet Gynecol Reprod Biol 2013;167:210-4.
28. Gutl P, Greimel ER, Roth R, Winter R. Women's sexual behavior, body image and satisfaction with surgical outcomes after hysterectomy: a comparison of vaginal and abdominal surgery. J Psychosom Obstet Gynaecol 2002;23:51-9.
29. Hehenkamp WJ, Volkers NA, Bartholomeus W, de Blok S, Birnie E, Reekers JA, et al. Sexuality and body image after uterine artery embolization and hysterectomy in the treatment of uterine fibroids: a randomized comparison. Cardiovasc Intervent Radiol 2007;30:866-75.

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Impact of laparoscopic ovarian drilling on serum anti-mullerian hormone levels in patients with anovulatory Polycystic Ovarian syndrome

Anovulatuvar Poliskistik Over sendromu olan hastalarda laparoskopik over delmenin serum anti-mullerian hormon düzeyleri üzerine etkisi

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Abstract

Objectives: Anti-mullerian hormone (AMH) is a marker of the activity of recruitable ovarian follicles. It is useful in the prediction of ovarian reserve. Women with polycystic ovarian syndrome (PCOS) have elevated circulating and intrafollicular AMH levels. Laparoscopic ovarian drilling (LOD) in patients with PCOS destroys ovarian androgen-producing tissue and reduces their peripheral conversion to estrogens. Identifying factors that determine the response of patients with PCOS to LOD will help in selecting the patients who would likely benefit from this treatment. AMH is one such marker that can predict the response to LOD. To evaluate the effect of LOD on serum AMH levels among PCOS responders and non-responders and the usefulness of AMH as a tool in predicting the response to LOD, and to whether there was loss of ovarian function after LOD.

Materials and Methods: This is a prospective cohort study including 30 clomiphene-resistant women with anovulatory PCOS undergoing LOD. Statistical analysis was performed to evaluate the effect of LOD on serum levels of AMH on these women.

Results: A significant fall in the levels of AMH was observed after LOD in both responders and non-responders ($p<0.001$). Women with AMH >8.3 ng/mL showed a significantly lower ovulation rate (33.3%). LOD was not associated with a risk of diminished ovarian reserve.

Conclusion: LOD is an effective first-line treatment for women with PCOS who are clomiphene resistant. LOD has no negative effect on ovarian reserve. AMH is a useful marker in predicting the outcome of LOD.

Keywords: Anti-mullerian hormone, laparoscopic ovarian drilling, ovarian reserve, polycystic ovarian syndrome

Öz

Amaç: Anti-mullerian hormon (AMH) toplanabilir over foliküllerinin aktivitesinin bir göstergesidir. Over rezervinin tahmin edilmesinde faydalıdır. Polikistik over sendromu (POS) olan kadınlarda dolaşımdaki ve folikül içindeki AMH düzeyleri yükselmiştir. Laparoskopik over delme (LOD) POS'lu hastalarda ovarian androjen üreten dokuyu harap eder ve östrojenlere periferal dönüşümünü azaltır. POS hastalarının LOD'ye yanıtını belirleyen faktörlerin ortaya konması bu tedaviden yarar görebilecek hastaları seçmeye yardımcı olacaktır. AMH LOD'ye yanıtı öngördürebilen böyle bir belirteçtir.

POS'ye yanıt veren ve vermeyen hastalarda LOD'nin serum AMH düzeyleri üzerine etkisini ve LOD'ye yanıtın bir belirteci olarak AMH'nin kullanışlılığını değerlendirmek ve LOD'den sonra over fonksiyonlarında kayıp olup olmadığını görmek.

Gereç ve Yöntemler: Bu çalışma LOD yapılan, anovulatuvar POS olan, klomifene dirençli 30 kadını kapsayan prospektif bir kohort çalışmasıdır. Bu çalışmada, kadınlarda LOD'nin serum AMH düzeylerine etkisini değerlendirmek için istatistiksel analiz yapılmıştır.

Bulgular: Hem yanıt verenlerde, hem de vermeyenlerde LOD'den sonra AMH düzeylerinde belirgin düşme gözlendi ($p<0,001$). AMH >8,3 ng/mL olan kadınlarda ovülasyon hızı belirgin olarak daha düşüktü (%33,3). LOD azalmış over rezervi ile ilişkili değildi.

Sonuç: LOD klomifen direnci olan POS'lu kadınlarda etkili bir birinci sıra tedavidir. LOD'nin over rezervi üzerine herhangi bir olumsuz etkisi yoktur. AMH LOD'nin sonucunu öngörmede faydalı bir belirteçtir.

Anahtar Kelimeler: Anti-mullerian hormon, laparoskopik over delme, over rezervi, polikistik over sendromu

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Introduction

Polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorders of women in the reproductive age group, affecting about 4 to 12% of women worldwide[1]. It is characterized by a combination of hyperandrogenism (either clinical or biochemical), chronic anovulation and polycystic ovaries, and is frequently associated with insulin resistance and obesity. The underlying cause of PCOS is unknown. However, a genetic basis that is both multifactorial and polygenic is suspected, because there is well documented aggregation of the syndrome within families[2].

Anti-mullerian hormone (AMH), also known as mullerian-inhibiting substance, was until recently, known mainly as a substance involved in male sexual differentiation. AMH is now considered as a marker that can estimate the quantity and activity of recruitable follicles in early stages of growth, thus being more reliable for the prediction of ovarian reserve. Women with PCOS have about 2-3 times elevated circulating and intrafollicular AMH levels. There are controversial data regarding whether the AMH excess in PCOS is related to the increment in the number of preantral follicles or due to an intrinsically increased production by granulosa cells. However, the increase may also be a consequence of other factors in PCOS such as hyperandrogenism and insulin resistance[3,4]. This increased AMH is associated with retardation of follicular development.

The principle behind laparoscopic ovarian drilling (LOD) in patients with PCOS is to destroy ovarian androgen-producing tissue and reduce peripheral conversion of androgens to estrogens. Specifically, a fall in serum levels of androgens and luteinizing hormone (LH) and an increase in the level of follicle-stimulating hormone (FSH) have been demonstrated after ovarian drilling[5,6]. The endocrine changes following surgery are thought to convert the adverse androgen dominant intra-follicular environment to one that is estrogenic, and to restore the normal hormonal environment by correcting ovarian pituitary feedback[7].

Identifying factors that determine the response of women with PCOS to LOD will help in selecting the patients who are likely to benefit from this treatment, thus avoiding fruitless treatment and improving success rate. The consistency of serum levels of AMH throughout the menstrual cycle, with very little inter cycle variability, makes it an attractive marker of response to treatment. With this background, we conducted a prospective cohort study to evaluate the effect of LOD on plasma levels of AMH in PCOS.

Materials and Methods

This is a prospective cohort study on clomiphene citrate (CC)-resistant women with anovulatory PCOS. The study was conducted in a 300-bed super specialty obstetrics and gynecology hospital and in vitro fertilization center. The women included in the study were aged between 18 to 35 years. This study was conducted over a period of one year (April 2013 to April 2014) and included 30 women who were infertile and anovulatory with CC resistant PCOS. Each woman underwent LOD. The primary outcomes were the effect of LOD on serum AMH levels and the difference between AMH levels in responders (women who ovulated) and non-responders (no ovulation). The secondary outcomes studies were the usefulness of AMH as a tool in evaluating the outcome of LOD and to assess the ovarian reserve after LOD. PCOS was diagnosed based on the 2003 Rotterdam European Society for Human Reproduction/American Society of Reproductive Medicine criteria[8]. The women were followed up for a year after undergoing LOD and evaluated regarding the response to LOD in terms of ovulation and pregnancy, and also to determine whether there was any loss of ovarian function because of LOD.

All women included in this study had normal hysteron-salpingogram and their partners had normal semen analysis according to the World Health Organization criteria[9]. Blood samples were collected on day 2 of the cycle before and 1 week after LOD to measure plasma concentrations of AMH, luteinizan hormon (LH), follicle stimulating hormone (FSH), testosterone (T), sex hormone-binding globulin (SHBG), and free androgen index {T/SHBG x 100}.

Additional blood samples were collected 3 and 6 months after LOD for the measurement of AMH. Plasma samples were assayed for AMH in duplicate using a commercial enzyme-linked immunosorbent assay kit (Immunotech, Beckman-Coulter UK Ltd., High Wycombe, Buckinghamshire, United Kingdom) in accordance with the manufacturer's protocol. The sensitivity of the assay was 0.24 ng/mL. The intraassay and interassay variabilities were 5% and 8%, respectively.

Assays for LH and FSH were performed using an automated microparticle enzyme immunoassay (Abbott Axsymanalyser; Abbott Diagnostics). Assays for SHBG were performed using an automated chemiluminescent immunoassay (Immuliteanalyser; Diagnostic Products Corporation).

LOD was perfomed under general anesthesia using a monopolar electrocautery needle. Four punctures were made per ovary at a power setting of 40 W for 4-6 seconds at each point. If the patient did not ovulate after LOD, CC would be started 6-8 weeks after surgery on days 2-6 of the menstrual cycle.

Ovulation was diagnosed by serial sonographic monitoring of follicular growth and follicular collapse with elevated serum progesterone levels 7 days later. The occurrence of ovulation or clinical pregnancy during a period of 6 months were noted. Pregnancy was diagnosed through a positive quantitative β-hCG and a definite gestational sac in an ultrasound examination.

Hormonal values were expressed as mean ± standard deviation. Comparison of values before and after LOD was performed using Student's paired t-test. Comparison of values between responders and non-responders was made using Student's independent t-test. All p-values less than 0.05 were considered significant.

Results

The mean age of the participants was 28.3±3.5 years. The study cohort women were obese, as reflected by a high body mass index (BMI) and waist:hip ratio. Serum levels of AMH, LH, testosterone, and the LH:FSH ratio were higher in non-responders than responders before laparoscopy (Figure 1). About 80% (24/30) of women with PCOS responded to LOD as evidenced by spontaneous ovulation. The pregnancy rate was 41.66% (10/24). About 20.0% (6/30) women with PCOS were still resistant to LOD. About 58.33% (14/24) did not conceive despite the high ovulation rate (80%).

Significant differences in AMH levels were observed between responders and non-responders before and after laparoscopy (p<0.001). Plasma levels of testosterone were significantly lower in responders when compared with non-responders (no ovulation). There was no significant difference in LH, LH:FSH between responders and non-responders both before and after LOD (Table 1 and 2). As a result of LOD, significant reductions in levels of AMH were observed in both responders and non-responders, but the magnitude of change was significantly higher in responders (p<0.001) when compared with non-responders (p<0.028) (Figure 2). There was no significant change in the levels of FSH in both responders and non-responders after LOD. No significant correlation was observed between plasma levels of AMH and age, BMI, LH or FSH. There was a significant positive correlation noted between plasma AMH and testosterone levels (any statistical test?). LOD led to reduced levels of AMH in patients with PCOS, but these changes were not statistically significant and only indicated the patient's normality and had no negative impact on ovarian reserve.

A cut-off level of AMH was identified as 8.3 ng/mL, above which the chances of ovulation seemed to be significantly reduced. Women with AMH >8.3 ng/mL showed a significantly

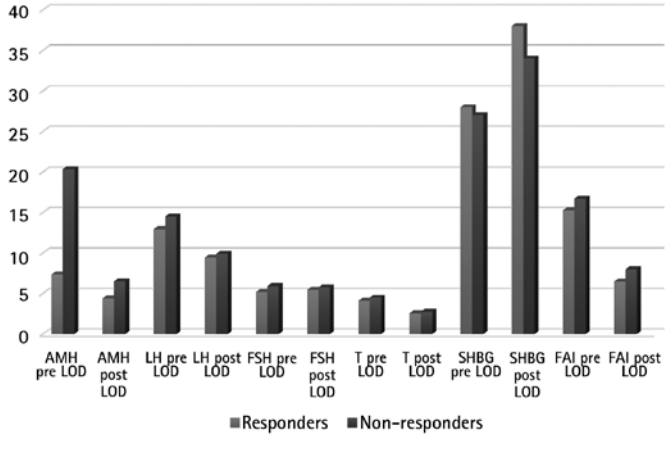

Figure 1. Comparison of variables among responders and non-responders before and after laparoscopic ovarian drilling

LH: Luteinizing hormone, FSH: Follicle-stimulating hormone, AMH: Anti-mullerian hormone, T: Testosterone, SHBG: Sex hormone-binding globülin, FAI: Free androgen index, LOD: Laparoscopic ovarian drilling

Table 1. Comparison of variables between responders and non-responders before laparoscopic ovarian drilling

Variable	Responders (n=24) median (interquartile range)	Non-responders (n=6) median (interquartile range)	p
AMH	7.350 (7.8-5.825)	20.350 (25.025-16.50)	<0.001
LH	12.94 (13.995-11.39)	14.50 (18.45-12.72)	0.097
FSH	5.180 (5.60-4.35)	5.91 (6.840-5.163)	0.055
LH:FSH	2.585 (2.90-2.282)	2.610 (2.75-2.29)	0.917
T	4.11 (4.40-3.84)	4.50 (4.463-4.475)	0.009
SHBG	28 (34.25-23.12)	27.50 (28.0-22.25)	0.603
FAI	15.28 (18.93-12.05)	16.71 (20.56-15.97)	0.162

p<0.05 significant, LH: Luteinizing hormone, FSH: Follicle-stimulating hormone, AMH: Anti-mullerian hormone, T: Testosterone, SHBG: Sex hormone-binding globülin, FAI: Free androgen index

Table 2. Comparison of different variables between responders and non-responders after laparoscopic ovarian drilling

Variable	Responders (n=24) median (interquartile range)	Non-responders (n=6) median (interquartile range)	P
AMH	4.40 (4.8-3.8)	6.50 (7.20-5.70)	<0.001
LH	9.45 (10.0-8.60)	9.90 (11.15-8.90)	0.253
FSH	5.450 (5.63-5.005)	5.750 (6.765-5.263)	0.176
LH:FSH	1.695 (1.888-1.530)	1.750 (1.818-1.603)	0.959
T	2.55 (2.875-2.250)	2.750 (3.050-2.638)	0.191
SHBG	38 (44.75-36.0)	34 (38.25-33.0)	0.065
FAI	6.480 (7.558-5.585)	7.995 (9.30-7.060)	0.036

p<0.05 is significant, LH: Luteinizing hormone, FSH: Follicle-stimulating hormone, AMH: Anti-mullerian hormone, T: Testosterone, SHBG: Sex hormone-binding globülin, FAI: Free androgen index

(p<0.001) lower ovulation rate (33.3%) than that of women with AMH <8.3 ng/mL (100%). Significant differences were observed in AMH levels before and after LOD, which may indicate a possible diminished ovarian reserve. Although the AMH values after LOD were found lower than those before LOD, the after values stayed higher than normal when compared with normal women without PCOS.

Discussion

The present study shows a positive correlation between plasma AMH and testosterone values in anovulatory women with PCOS. This agrees with the study conducted by Poujade O et al and many others[10]. This positive association is explained by the stimulatory effect of androgens on the primodial follicular growth and granulosa cell proliferation that increases AMH secretion, or the inhibitory effect of AMH on aromatase activity, leading to an increase in androgens[10,11]. Another cause for the increase in AMH and androgens in PCOS is secondary to hyperinsulinemia, because it enhances gonadotropin-stimulated steroid production in granulosa and theca cells. A possible explanation for the 58.33% of women with PCOS not conceiving, despite the high ovulation rate after LOD, is that the amount of ovarian tissue destroyed during LOD may not have been enough to induce favorable changes on reproductive parameters by reducing intraovarian AMH to a level consistent with resumption of ovulation. This study shows a significant decrease in serum testosterone, LH, and LH:FSH ratio, one week after LOD. These findings are in agreement with many previous studies[12,13]. Although the after LOD values were found lower than the before LOD values with ovarian reserve markers, the after values remained higher in non-responders when compared with the responders. Previous studies have shown that the ovarian reserve in women with PCOS was found higher than in women with normal menstruation[13].

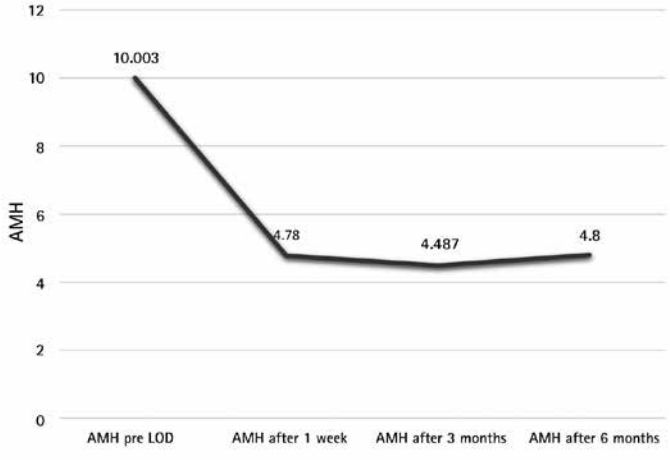

Figure 2. Anti-mullerian hormone values before and after laparoscopic ovarian drilling among polycystic ovarian syndrome women

AMH: Anti-mullerian hormone, LOD: Laparoscopic ovarian drilling

It can be deduced from earlier studies that LOD normalizes ovarian function, which is significant in follicular recruitment and maturation, and has no negative effect on ovarian reserve. It seems that the ovarian tissue damage occurs during and continues only for a short period after LOD, as evidenced by the fact that the AMH and FSH levels did not correlate with time since LOD[13,14]. The reduction in AMH levels results from the bilateral diathermy technique where the androgen producing stroma is destroyed. There is a decrease in ovarian stromal blood flow and subsequently vascular endothelial growth factor and insulin-like growth factor 1, which are high in PCOS. In our study, LOD appeared not to be associated with an increased risk of diminished ovarian reserve. Most of the changes in ovarian reserve markers in the current work after LOD could be interpreted with the normalization of ovarian function in the enrolled women with PCOS rather than the reduction of ovarian reserve.

Similar to the study by Api[15], we found that the ovarian reserve of patients with PCOS did not change significantly after LOD, and the reduction of AMH after LOD may be referred to as the normalization of women with PCOS after LOD. Thus, the likelihood of traumatic injury to ovaries as because of LOD is negligible. Overall, it seems that although LOD leads to a reduction in AMH levels in women with PCOS, these are not statistically significant and only indicate the patient's normality and has no negative impact on ovarian reserve[15].

Conclusion

Based on the results of this study, LOD is recommended as an effective first-line treatment in women with PCOS who are anovulatory and clomiphene resistant. LOD has no negative effect on ovarian reserve, as shown by the markers of ovarian reserve such as FSH and AMH during the follow-up period. It is also recommended that women who are candidates for undergoing LOD may benefit from the measurement of serum AMH concentration to determine their likelihood of response to LOD. Women found to have high serum AMH levels (>8.3 ng/mL) can be counselled about the lower chances of responding to LOD. It is also recommended that using AMH as a reliable marker of ovarian reserve and measuring it in women with anovulatory PCOS undergoing LOD may provide a tool for predicting the outcome of LOD.

Ethics

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Peer-review: Internally peer-reviewed

References

1. Asuncion M, Calvo RM, San Millan JL, Sancho J, Avila S, Escobar-Morreale HF. A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. J Clin Endocrinol Metab 2000;85:2434-8.

2. Franks S, Gharani N, Waterworth D, Batty S, White D, Williamson R, et al. The genetic basis of polycystic ovary syndrome. Hum Reprod 1997;12:2641-8.
3. Pigny P, Merlen E, Robert Y, Cortet-Rudelli C, Decanter C, Jonard S, et al. Elevated serum level of anti-mullerian hormone in patients with polycystic ovary syndrome: relationship to the ovarian follicle excess and to the follicular arrest. J Clin Endocrinol Metab 2003;88:5957-62.
4. Laven JS, Mulders AG, Visser JA, Themmen AP, De Jong FH, Fauser BC. Anti-Mullerian hormone serum concentrations in normoovulatory and anovulatory women of reproductive age. J Clin Endocrinol Metab 2004;89:318-23.
5. Armar NA, McGarrigle HH, Honour J, Holownia P, Jacobs HS, Lachelin GC. Laparoscopic ovarian diathermy in the management of anovulatory infertility in women with polycystic ovaries: endocrine changes and clinical outcome. Fertil Steril 1990;53:45-9.
6. Greenblatt E, Casper RF. Endocrine changes after laparoscopic ovarian cautery in polycystic ovarian syndrome. Am J Obstet Gynecol 1987;156:279-85.
7. Aakvaag A, Gjonnaess H. Hormonal response to electrocautery of the ovary in patients with polycystic ovarian disease. Br J Obstet Gynaecol 1985;92:1258-64.
8. Rotterdam EA-SPCWG. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 2004;81:19-25.
9. WHO. World Health Organization Laboratory Manual for the Examination and Processing of Human Semen. Geneva: World Health Organization 2010.
10. Poujade O, Gervaise A, Faivre E, Deffieux X, Fernandez H. Surgical management of infertility due to polycystic ovarian syndrome after failure of medical management. Eur J Obstet Gynecol Reprod Biol 2011;158:242-7.
11. Maheshwari A, Gibreel A, Bhattacharya S, Johnson NP. Dynamic tests of ovarian reserve: a systematic review of diagnostic accuracy. Reprod Biomed Online 2009;18:717-34.
12. El Behery MM, Diab AE, Mowafy H, Ebrahiem MA, Shehata AE. Effect of laparoscopic ovarian drilling on vascular endothelial growth factor and ovarian stromal blood flow using 3-dimensional power Doppler. Int J Gynaecol Obstet 2011;112:119-21.
13. Chang HJ, Han SH, Lee JR, Jee BC, Lee BI, Suh CS, et al. Impact of laparoscopic cystectomy on ovarian reserve: serial changes of serum anti-Mullerian hormone levels. Fertil Steril 2010;94:343-9.
14. Amer SA, Li TC, Ledger WL. The value of measuring anti-Mullerian hormone in women with anovulatory polycystic ovary syndrome undergoing laparoscopic ovarian diathermy. Hum Reprod 2009;24:2760-6.
15. Api M. Is ovarian reserve diminished after laparoscopic ovarian drilling? Gynecol Endocrinol 2009;25:159-65.

Case Report / Olgu Sunumu

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True management of Obstructed Hemi-vagina and Ipsilateral Renal Anomaly syndrome

Obstrükte Hemivajina ve İpsilateral Renal Anomali sendromunun doğru yönetimi

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Abstract

Herlyn-Werner-Wunderlich syndrome is an unusual congenital anomaly of the female genitourinary system, which is described as uterine didelphys with Obstructed Hemi-vagina and Ipsilateral Renal Anomaly (OHIRA), also known as OHVIRA syndrome. Typical symptoms are pelvic pain, tenderness, pelvic mass due to blood collection in the obstructed hemi-vagina and uterus, and dysmenorrhea that usually begins shortly after menarche. Clinical suspicion is very important for diagnosis and correct management avoids both short- and long-term complications. Surgical removal of the vaginal septum is the main treatment method. Herein, we describe the evaluation and surgical management of a patient with OHVIRA syndrome who was diagnosed using magnetic resonance imaging and pelvic ultrasound.

Keywords: Hematometrocolpos, mullerian duct anomaly, obstructed hemi-vagina and ipsilateral renal anomaly syndrome, uterus didelphys

Öz

Herlyn-Werner-Wunderlich sendromu kadın genitoüriner sistemini tutan nadir bir konjenital anomalidir. Uterus didelfis ile birlikte Obstrükte Hemi-Vajina ve İpsilateral Renal Anomali (OHVIRA) ile seyreder ve OHVIRA sendromu olarak da bilinir. Tipik belirtileri arasında obstrükte hemi-vajen ve uterus nedeniyle kan birikimine bağlı menarştan kısa süre sonra başlayan pelvik ağrı, gerginlik, pelvik kitle ve dismenore yer alır. Tanı için klinik şüphe çok önemlidir ve doğru yönetimi ile kısa ve uzun dönem komplikasyonların önüne geçilebilir. Esas tedavi yöntemi vajinal septumun açılmasıdır. Burada manyetik rezonans görüntüleme ve pelvik ultrason ile OHVIRA sendromu tanısı konulan bir hastanın değerlendirilmesi ve cerrahi yönetimi sunulacaktır.

Anahtar Kelimeler: Hematometrokolpos, mülleryan kanal anomalisi, obstrükte hemi-vajina ve ipsilateral renal anomali sendromu, uterus didelfis

PRECIS: The management of a girl aged 13 years with obstructed hemivagina and ipsilateral renal anomaly syndrome is presented.

Introduction

Obstructed hemi-vagina and ipsilateral renal anomaly (OHVIRA) syndrome, traditionally known as Herlyn-Werner-Wunderlich syndrome, is a rare clinical entity of Müllerian anomalies, which has been reported as case reports since 1922. Obstructive mullerian anomalies are estimated to affect approximately 0.1-3.8% of the female population[1]. It mainly presents with cyclical and or chronic pelvic pain and pelvic swelling while having regular cycles due to hematometrocolpos in the obstructed hemi-vagina. The classic presentation of OHVIRA syndrome is that of a postmenarchal girl with remittent pelvic pain, usually associated with menstruation, and a vaginal bulge on pelvic examination and/or foul discharge. The growing experience of OHVIRA syndrome in literature has familiarized physicians with this condition. However, delays in diagnosis are still a concern that may lead to complications such as chronic infection, endometriosis, and adhesions, which result in subfertility or infertility. Herein, we describe the evaluation and surgical management of a girl with OHVIRA syndrome who was diagnosed using magnetic resonance imaging (MRI) and pelvic ultrasound examination.

Case Report

A girl aged 13 years was referred to our hospital because of cyclical pain in the lower abdomen, which she had had for the last two months, hindering her daily activities.

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The patient denied having any recent abdominal trauma, vomiting or diarrhea, and menarche had occurred at age 12 years. She was not sexually active and under any medical treatment. The laboratory tests including complete blood count, tumor markers, and beta human chorionic gonadotropin were within normal ranges. An abdominal ultrasound examination revealed absence of the left kidney and a cystic mass adjacent to the uterus that filled the left half of the pelvis. The uterus was of normal size and shape with myometrium, cervix, and vagina. The abdominopelvic MRI scan demonstrated an enlarged mass consistent with hematometrocolpos, a uterus didelphys, along with left renal agenesis (Figures 1, 2). In the hospital where she was first admitted, a suprapubic catheter was placed into the left obstructed hemi-vagina under ultrasound guidance by the department of interventional radiology. Although the hematometrocolpos was drained, it was not a definitive treatment. On admission to our clinic, she had no pain but a suprapubic catheter that was sutured to skin. The external genitalia were normal. After the patient and her family were informed, vaginal examination was performed under general anesthesia. Vaginoscopy and hysteroscopy were performed in the lithotomy position without hymenotomy. The left hemi-vagina was blunt. After clear visualization of the right vagina, the vaginal septum was dissected using a hysteroscopic unipolar needle electrode. The left hemi-vaginal and uterine cavities were observed, along with the suprapubic drainage catheter (Figure 3). The supra-pubic catheter placed in the left obstructed hemi-vagina was gently removed. The vaginal septum was then dissected longitudinally using a unipolar needle electrode. After dissection, a 3-cm gap in the vaginal septum was obtained, which allowed drainage from the left uterine cavity (Figure 4). The patient tolerated the procedure

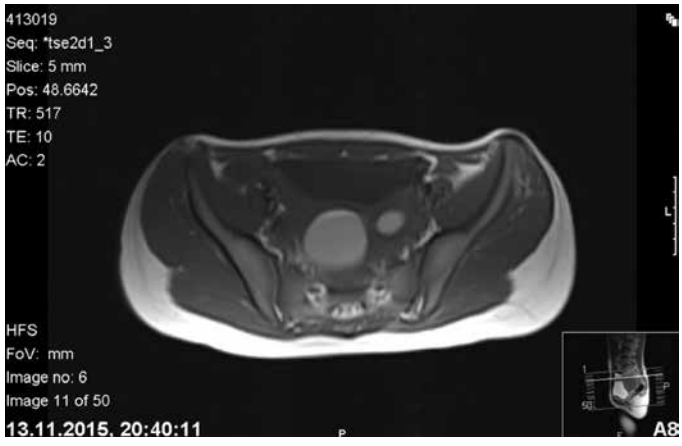

Figure 1. Magnetic resonance image demonstrating uterus didelphys with left hematometrocolpos

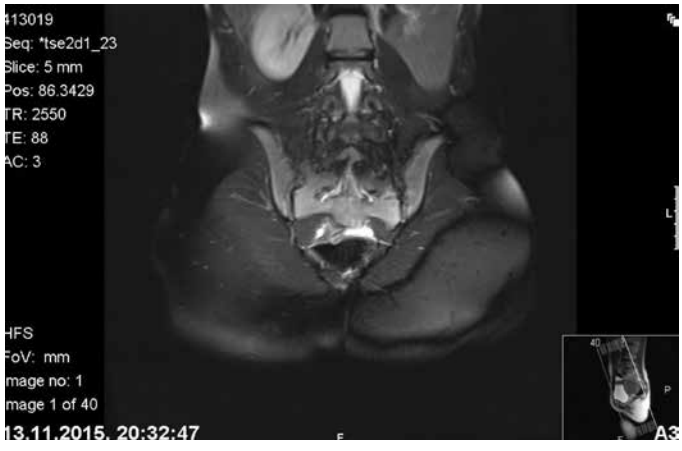

Figure 2. Magnetic resonance image demonstrating left renal agenesis

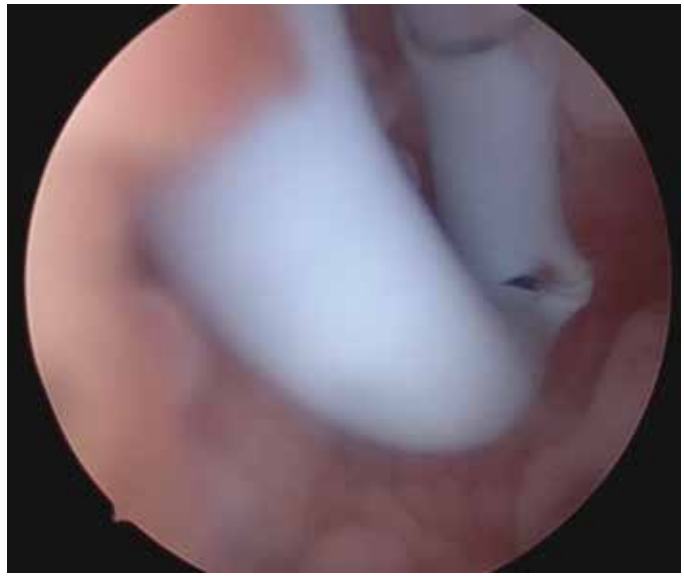

Figure 3. Suprapubic drainage catheter placed in the left obstructed hemi-vagina

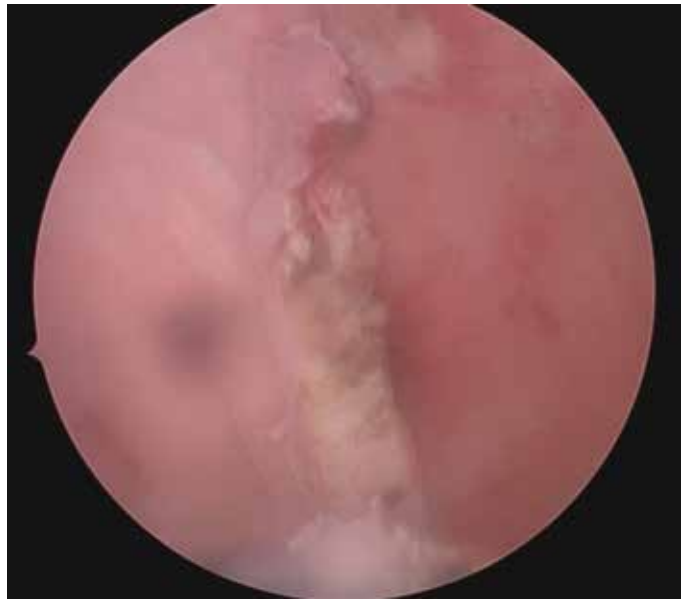

Figure 4. Vaginal septum and both vaginal spaces after dissection with a unipolar needle electrode

well and was discharged from hospital the next day. The first follow-up visit was four weeks after the operation. She had no symptoms and no complications were observed. At the sixth month follow-up visit she reported regular and painless menstrual cycles. On ultrasound examination, no distension was observed in the uterine horns or vagina.

Discussion

The Müllerian duct develops craino-caudally and fuses between the 6th and 22nd gestational weeks. The prevalence of Müllerian anomalies is an issue that remains to be clarified. Discrepancies of diagnostic modalities, classification systems, terminologies, and population characteristics amongst available studies rendered this issue confounding. The estimated prevalence ranges from 0.1% to 3.8%[1]. According to a largely accepted hypothesis, OHVIRA syndrome is caused by an embryonic arrest at about the 8th gestational week[2,3]. It seems that an injury on the caudal portion of the mesonephric (Wolffian) duct subsequently leads to malformation and malfusion of Müllerian ducts. Injury on the mesonephric duct also results with renal anomalies. However, there are some reported cases with obstructed hemi-vagina, double uterus, and normal urinary systems, which seem to conflict with this hypothesis. Patients present with pelvic pain, dysmenorrhea, pelvic mass, and rarely with complications such as pyocolpos, endometriosis, and infertility[4]. Most patients report a history of regular menses until the obstruction of the hemi-vagina resulted in distention and enlarged mass. Hence, physicians should suspect OHVIRA syndrome in young patients who present with these symptoms. Obstructed hemi-vagina and renal anomalies in OHVIRA syndrome are seen twice as frequently in the right side of the body compared with the left[5]. The estimated mean age of diagnosis was defined as 14 years in the literature[2]. This case had an unusual presentation considering the lateralization. These kinds of cases require a high amount of suspicion for diagnosis. Vaginal tissues are quite tense and the obstructed hemi-vagina may contain large amounts of blood. A sufficient enough absorption of blood between periods may prevent aggravation of the symptoms. Inability to perform vaginal examination on a virgin patient, lower accuracy of abdominal ultrasound, mild nature of symptoms, and lacking adequate amount of suspicion or experience may all contribute to delayed diagnosis and improper treatment, which may result in intra-abdominal infection and/or abscess. Early recognition is important in avoid complications.

In cases of OHVIRA, the vaginal septum is generally longitudinal and has variable thickness. Abdominal ultrasonography has been the preferred initial imaging modality; MRI should be considered for diagnosis and decision making if there is a suspicious morphology of the uterus and adnexa[2,3]. The association between OHVIRA syndrome and other urogenital abnormalities can be better evaluated using MRI. MRI is far better than ultrasound for characterizing anatomic relationships owing to its multiplanar capabilities and larger field of view. However, the gold standard for diagnosis is laparoscopy, which has the added benefit of performing therapeutic drainage of hematometra/hematocolpos, vaginal septotomy, and marsupialization. Treatment usually involves surgery in the form of excision of the vaginal septum, which helps to relieve the obstruction. Previously, a two-step surgical approach including drainage and resection of the septum was performed. Also, hymenotomy was favored for better visualization. However, with improved surgical capabilities, it is possible to complete the surgery in one procedure without hymenotomy. Prognosis is good, with the major concern being preservation of fertility. However, symptom recurrence due to vaginal adhesions is possible. In such a condition, silicon dilators can be used following re-resection[6]. Women with uterus didelphys have a high likelihood of becoming pregnant, with approximately 80% of patients able to conceive, but with elevated rates of premature delivery (22%) and abortion (74%); cesarean section is necessary in over 80% of patients[7]. Understanding the imaging findings is critical for early diagnosis in an attempt to prevent complications such as endometriosis or adhesions from chronic infections with subsequent infertility.

Conclusion

OHVIRA syndrome is a rare congenital anomaly with different clinical presentations. Ultrasound and MRI are the initial imaging modalities and laparoscopy is the gold standard for diagnosis. The main treatment modality is the resection of the vaginal septum through vaginoscopy without hymenotomy.

Ethics

Informed Consent: Consent form was filled out by the patient.
Peer-review: Externally and Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Cem Atabekoğlu, Yavuz Emre Şükür, Batuhan Turgay, Concept: Cem Atabekoğlu, Yavuz Emre Şükür, Design: Betül Yakıştıran, Cem Atabekoğlu, Data Collection or Processing: Betül Yakıştıran, Batuhan Turgay, Analysis or Interpretation: Cem Atabekoğlu, Yavuz Emre Şükür, Literature Search: Betül Yakıştıran, Writing: Betül Yakıştıran.
Conflict of Interest: No conflict of interest was declared by the authors.
Financial Disclosure: The authors declared that this study received no financial support.

References

1. Mehra S, Chamaria K, Garga UC, Kataria A, Ahuja A. Imaging Diagnosis of Herlyn-Werner-Wunderlich Syndrome- An Extremely Rare Urogenital Anomaly. J Clin Diagn Res 2015;9:06-8.

2. Nigam A, Raghunandan C, Yadav R, Tomer S, Anand R. OHVIRA syndrome: rare cause of chronic vaginal discharge in an unmarried female. Congenit Anom (Kyoto) 2011;51:153-5.
3. Cox D, Ching BH. Herlyn-Werner-Wunderlich syndrome: a rare presentation with pyocolpos. J Radiol Case Rep 2012;6:9-15.
4. Zivkovic K, Prka M, Zivkovic N, Bucko A, Habek D. Unusual case of OHVIRA syndrome with a single uterus, unrecognized before labor and followed by an intrapartal rupture of obstructed hemivagina. Arch Gynecol Obstet 2014;290:855-8.
5. Vercellini P, Daguati R, Somigliana E, Vigano P, Lanzani A, Fedele L. Asymmetric lateral distribution of obstructed hemivagina and renal agenesis in women with uterus didelphys: institutional case series and a systematic literature review. Fertil Steril 2007;87:719-24.
6. Koyama-Sato M, Hashida O, Nakamura T, Hirahara F, Sakakibara H. Case of early postoperative adhesion in a patient with molimina due to transverse vaginal septum concomitant with imperforate hymen. J Obstet Gynaecol Res 2015;41:1141-4.
7. Heinonen PK. Clinical implications of the didelphic uterus: long-term follow-up of 49 cases. Eur J Obstet Gynecol Reprod Biol 2000;91:183-90.

Case Report / Olgu Sunumu

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Postpartum aortic dissection in a patient without Marfan's syndrome

Marfan sendromu olmayan hastada postpartum aort diseksiyonu

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Abstract

Aortic dissection can occur in pregnancy or during the postpartum period without pre-existing disease and it is a rare but potentially life-threatening event. Herein, we present a young woman without Marfan's syndrome who developed a postpartum ascending aortic dissection 5 days after cesarean section.
Keywords: Aortic dissection, Marfan's syndrome, postpartum

Öz

Aort diseksiyonu hamilelikte veya postpartum dönemde önceden varolan hastalık olmadan da görülebilen nadir görülen ve hayatı tehdit eden bir klinik durumdur. Biz bu olgu sunumunda Marfan sendromu olmayan genç bir kadında sezaryenden sonraki 5. gün gelişen postpartum aort diseksiyonunu sunduk.
Anahtar Kelimeler: Aort diseksiyonu, Marfan sendromu, postpartum

Introduction

Aortic dissection is the separation of the aortic wall layers and formation of a true lumen and a false lumen. Acute aortic dissection in pregnant women is a rare but potentially life-threatening event. It is usually related to severe hypertension due to preeclampsia, coarctation of the aorta or connective tissue disorders such as Marfan's syndrome. Aortic dissection may occur at any time during gestation (5% in the first trimester, 10% in the second trimester, 50% in the third trimester, and 20% postpartum)[1]. Postpartum aortic dissection occurs between day 1 and day 42 after either vaginal or cesarean section delivery. We report a young woman without Marfan's syndrome who developed postpartum ascending aortic dissection 5 days after she delivered a healthy female infant by cesarean section.

Case Report

A multiparous women aged 40 years who had an uneventful cesarean section 5 days previously was admitted to the emergency department with severe chest and back pain. According to information gained from the patient, she had regular antenatal checkups, she had no history of serious illness (chronic hypertension, cardiac disease, kidney disease, or connective tissue disorder), operations, or hospitalization. She had no family history of connective tissue diseases or signs of Marfan's syndrome, and did not have preeclampsia or perinatal or prior heart disease. When she arrived at the hospital, her blood pressure was 160/60 mmHg, heart beat was 65 beats per minute, electrocardiography was normal, and D-dimer was high (2.860 ng/mL). The patient was referred to our hospital with a diagnosis of pulmonary embolism. Thoracal computed tomography angiography (CTA) showed type A aortic dissection (Figure 1). There was a dissection flap that started from the ascending aorta and extended into the iliac arteries. The diameter of ascending aorta was 43 mm. Transthoracic echocardiography revealed that her ejection fraction was 65%, and there was minimal regurgitation of the aortic valve. She was taken to the operating room.

Under deep hypothermic circulatory arrest, an ascending aortic replacement was performed. Four hours postoperatively, she was taken into surgery again due to major bleeding and hypotension. Surgery revealed that the dissection had progressed to the aortic root. Cardiopulmonary bypass was begun, and a Bentall operation was performed. Unfortunately, the patient could not tolerate this second operation and died of uncontrollable bleeding.

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Discussion

Aortic dissection can occur in pregnancy or during the postpartum period without pre-existing disease due to hormonal changes, regardless of whether delivery was vaginal or by cesarean section. After hypertension and Marfan's syndrome, pregnancy is the most common risk associated with aortic dissection, a potentially deadly event.

The increase of estrogen and progestogen in the third trimester of pregnancy may add additional risk because the aorta expresses oestrogen and progestogen receptors[2]. Peripartum hormonal changes can cause fragmentation of reticular fibers, decreases in the amount of acid mucopolysaccharides, and damage to the normal shapes of elastic fibers, thereby increasing the risk of aortic dissection. These changes in the structure of the aorta during pregnancy have been reported to be similar to the medial degeneration pattern found in patients with aortic dissection.

Cardiovascular stresses such as pressure, heart rate, stroke volume, cardiac output, left ventricular mass, and blood volume are increased by pregnancy, and may cause hemodynamic stress on the aortic wall[2]. With the termination of puerperal uteroplacental circulation and uterine contraction, along with interstitial fluid absorption, the circulating volume could be increased by 15-25% within 72 h of delivery in a postpartum woman[3]. Thus, the third trimester of pregnancy or immediate postpartum stage is the most common interval during which aortic dissection occurs.

During pregnancy, the aorta and the vessel wall structures are generally weaker and more sensitive to hemodynamic forces. These pregnancy-related hemodynamic stresses and hormonal changes are the main factors for the development of aortic dissection[4]. CTA and transesophageal echocardiogram are the gold standard for the diagnosis of aortic dissection. CTA provides important information about the extent of dissection, the relation between the true and false lumen, and aortic branch compromise.

The complications of aortic dissection are aortic rupture, aortic regurgitation, acute myocardial infarction, tamponade, and end-organ ischemia. Back pain, chest pain, lower extremity ischemia and paraplegia are common symptoms of aortic dissection. If dissection involves the great vessels to the brain, loss of consciousness or signs of stroke may be seen. Survival is directly related to the timing of emergency intervention because the mortality rate increases 1 to 2% every hour during the first 24 to 48 hours after dissection[5]. Open surgical repair of type A dissections is recommended.

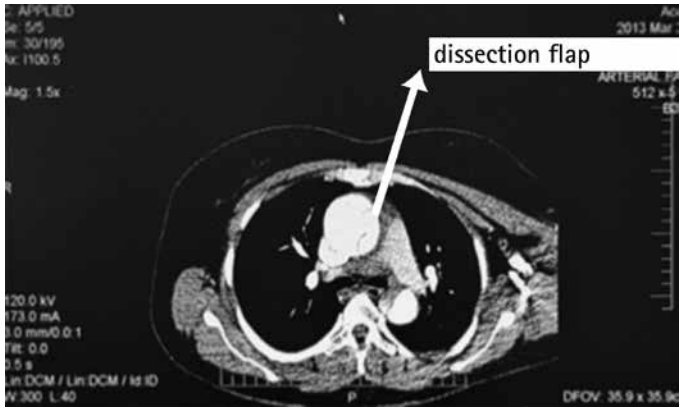

Figure 1. The computed tomography angiography showing the dissection

Yuan[3] evaluated 27 patients with postpartum aortic dissection. Pain was the most common symptom at onset, as it was in our petient. Sixteen (59.3%) patients had type A aortic dissections and four (14.8%) died[3].

Yang et al.[6] reported 11 paients who had aortic dissection during the course of pregnancy or puerperium. They found 6 patients during the postpartum stage, 4 of whom had type A aortic dissections and 2 died. Immer et al.[7] reported 5 patients with postpartum type A aortic dissections, one patient died.

Late presentation, delayed or misdiagnosis may be associated with postpartum aortic dissection because of its rarity[8]. The differential diagnoses of severe chest pain include acute myocardial infarction, pulmonary embolism, and aortic dissection[8]. Normal electrocardiogram cardiac enzymes are needed to exclude myocardial infarction. Normal coagulation test results and D-dimer level help rule out pulmonary embolism; the level of D-dimer was high in our case.

In the present case, the cause of death was the progress of dissection and uncontrolled bleeding. The patient reported here was known to have had normal blood pressure throughout her pregnancy and had no risk factors such as trauma, smoking, drug or alcohol abuse. She also had no family history of Marfan's syndrome.

Conclusion

This case suggests that acute aortic dissection can occur postpartum in young women who are normotensive and without Marfan's syndrome. Therefore, it is important to consider aortic dissection as a possible diagnosis during pregnancy and also after delivery. Aortic dissection is easily misdiagnosed as other cardiac, muscular, neurologic, esophageal or renal diseases because it may present with different clinical symptoms, such as back, chest, epigastric and abdominal pain, and cardiac arrest, which could potentially lead to the death of a new mother. Thus, obstetricians should consider aortic dissection as a possible diagnosis when these symptoms present in a postpartum woman.

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Ethics

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Authorship Contributions

Surgical and Medical Practices: Mihriban Yalçın, Melih Ürkmez, Concept: Mihriban Yalçın, Design: Kaptanı Derya Tayfur, Data Collection or Processing: Serkan Yazman, Analysis or Interpretation: Mihriban Yalçın, Serkan Yazman, Literature Search: Mihriban Yalçın, Writing: Mihriban Yalçın.

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References

1. Wanga S, Silversides C, Dore A, de Waard V, Mulder B. Pregnancy and Thoracic Aortic Disease: Managing the Risks. Can J Cardiol 2016;32:78-85.
2. van Hagen IM, Roos-Hesselink JW. Aorta pathology and pregnancy. Best Pract Res Clin Obstet Gynaecol 2014;28:537-50.
3. Yuan SM. Postpartum aortic dissection. Taiwan J Obstet Gynecol 2013;52:318-22.
4. Gelpi G, Pettinari M, Lemma M, Mangini A, Vanelli P, Antona C. Should pregnancy be considered a risk factor for aortic dissection? Two cases of acute aortic dissection following cesarean section in non-Marfan nor bicuspid aortic valve patients. J Cardiovasc Surg (Torino) 2008;49:389-91.
5. Fuster V, Andrews P. Medical treatment of the aorta. I. Cardiol Clin 1999;17:697-715.
6. Yang G, Peng W, Zhao Q, Peng J, Xiang X, Chai X. Aortic dissection in women during the course of pregnancy or puerperium: a report of 11 cases in central south China. Int J Clin Exp Med 2015;8:11607-12.
7. Immer FF, Bansi AG, Immer-Bansi AS, McDougall J, Zehr KJ, Schaff HV, et al. Aortic dissection in pregnancy: analysis of risk factors and outcome. Ann Thorac Surg 2003;76:309-14.
8. Kang BH, Lee MA, Rhee YE, Noh HT. Unexpected acute aortic dissection after elective cesarean section delivery: report of a case and review of the literature. Korean J Obstet Gynecol 2011;54:696-700.

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Bilateral ovarian metastasis of a Klatskin tumor: A rare case

Klatskin tümörünün bilateral ovarian metastazı: Nadir bir olgu

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Abstract

Metastatic carcinomas of the ovary have an important place in all ovarian cancers and tumors. They can originate from many organs and systems and may metastasize to the ovary. The most common primary origin of metastasis is the gastrointestinal tract and then breast tissue. Cholangiocellular carcinomas involving the junction of the right and left bile ducts are called Klatskin tumors, and their metastases to the ovaries are very rare. A woman aged 54 years who had been treated previously for Klatskin tumor was admitted to our clinic due to bilateral ovarian masses and high serum calcium 19-9 levels. The preoperative approach, operative, and postoperative management of Klatskin tumor is presented.

Keywords: Klatskin tumor, metastatic ovarian tumor, cholangiocellular carcinoma

Öz

Metastatik over kanserleri tüm over kanserleri içinde önemli bir yere sahiptir. Overe bir çok sistem ve organdan metastaz olabilmektedir. Metastazın en sık primer orijini gastrointestinal sistemdir ve bunu meme izler. Sağ ve sol safra kanallarının kavşağını kapsayan kolanjiosellüler karsinomlara Klatskin tümörü denir ve overlere metastazı çok nadir görülür. Klatskin tümörü tanısıyla, bir yıl önce opere edilen 54 yaşındaki kadın hasta kliniğimize bilateral overyan kitle ve yüksek serum kalsiyum 19-9 nedeniyle başvurdu. Overlere nadiren metastaz yapan Klatskin tümörünün ameliyat öncesi, ameliyat ve ameliyat sonrası yönetimi sunulmuştur.

Anahtar Kelimeler: Klatskin tümörü, metastatik over tümörü, kolanjiosellüler karsinom

Introduction

Cholangiocellular carcinomas are rare adenocarcinoma tumors of the bile ducts that may arise anywhere along the biliary tree. Cholangiocellular carcinomas involving the junction of the right and left bile ducts are called Klatskin tumors[1]. Ovarian metastases of these tumors are very rare clinical presentations[2]. We report bilateral ovarian metastases of a Klatskin tumor because of its rarity, aggressive structure, and difficulties in its management.

Case Report

A gravida 4, parity two woman aged 54 years who was three years menopausal underwent surgery for cholangiocellular cancer, type B, one year ago (T3BN0, Stage 3B). She received gemcitabine and 5-fluorouracil infusion therapy every two weeks for 8 cycles and chemoradiation with 5-fluorouracil infusions after surgery. After one year, she was admitted to the emergency unit with the main symptoms of abdominal swelling and pain. An abdominal ultrasound scan revealed bilateral ovarian masses and she was referred to our gynecologic oncology section of the department of obstetrics and gynecology. The gynecologic examination of the external genitalia was compatibly normal regarding her age. Bimanual examination revealed a mass that filled the pelvis and extended to the umbilicus. Magnetic resonance imaging showed a cystic, hemorrhagic mass with polypoid protrusions from the cyst wall, measuring 105x95x65 mm, originating from the left ovary. There was also a tumor on the right ovary sized 3.5x4x5 cm, which shared the same properties. Hematologic and biochemical tests were normal. Serum tumor markers calcium (CA) 125 and CA 19-9 were 35.8 U/mL and 1782.7 U/mL, respectively. Upper and lower gastrointestinal system endoscopies were also found normal. She underwent a diagnostic laparotomy. A lobulated 18x20 cm mass that originated from the left ovary and filled the

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pelvis, and a 5x6-cm cystic septal lesion originating from the right ovary were observed in the lower abdomen (Figure 1). No tumor formation or implant was diagnosed in the pelvic peritoneum or in the upper abdomen. Peritoneal wash fluid and multiple peritoneal biopsies were taken from all quadrants. The left adnexal mass was excised and sent for frozen section examination. The result of frozen section examination was reported as a malignant tumor with mucinous features. Debulking surgery was performed. Microscopic examination of paraffin sections from bilateral ovaries and omentum revealed mucinous adenocarcinoma (Figure 2). Malignant cells were also observed in the peritoneal wash fluid. A pathologic evaluation was also performed by comparing the findings of the previous material diagnosed as Klatskin tumor with the wash fluid sample and it was observed that both materials had similar characteristics of the same tumor. Immunohistochemical marker tests were performed to determine the tumor's primary origin.

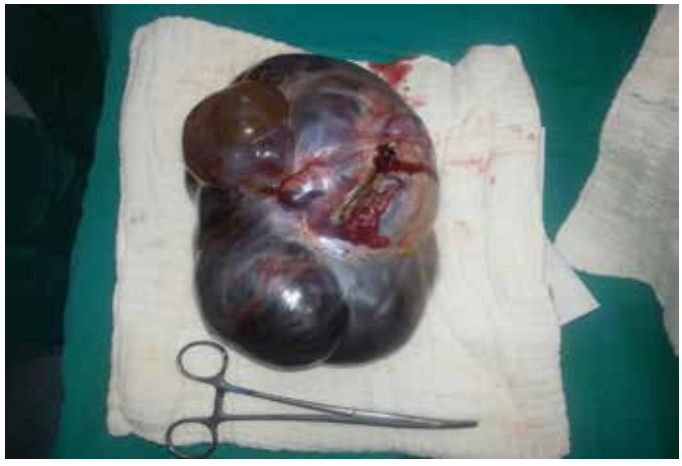

Figure 1. A lobulated metastatic mass originated from the left adnexa, measuring 18x20 cm

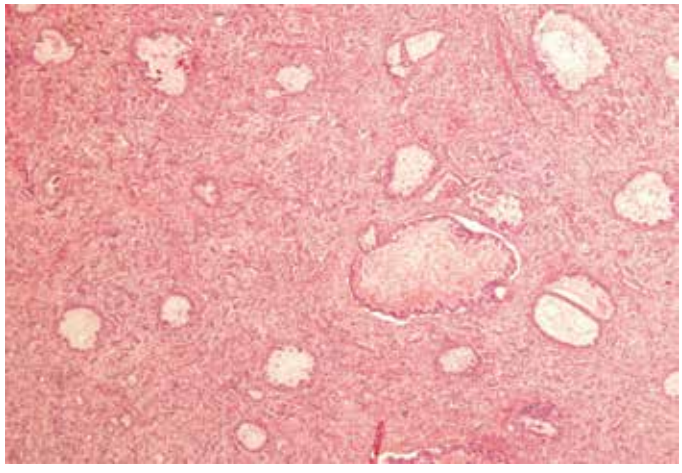

Figure 2. Mucinous adenocarcinoma. Atypical tumor cells containing mucin formed adenoid structures. Also, the stroma between tumor cells and the lumen of mucin formed adenoid structures is shown (hematoxylin&eosin, x100)

There was positive staining for CDX2, cytokeratin 19, and cytokeratin 20 detected in the tumor cells. Cytokeratin 7, PAX8, estrogen, and progesterone receptors were found negative. The immunohistochemical findings supported pancreaticobiliary and gastrointestinal origin. The final result of the pathologic examination confirmed a metastatic adenocarcinoma of the hepatic ducts.

Discussion

Ovarian cancer remains an important place among gynecologic cancers because of the high mortality rate. The ovaries are also the target organs for metastasis from many malignancies. Metastatic cancers of the ovary constitute 5-10% of total ovarian tumors, and 10-30%'s of total malignant ovarian tumors[2]. The incidence of metastatic ovarian tumors is increasing and the rates vary by countries. Frequency of metastatic ovarian cancer in Japan is reaching up to 40% because of high incidence of gastric cancers. However it is decreasing to 3% in Uganda[3]. In addition, the immunohistochemical markers which are used to diagnose the primary origin also contribute to increasing incidence[2].

The differential diagnosis of primary and metastatic tumors may be difficult. The pathological evaluation should be done with clinical evaluation in determining the primary origin. Metastatic ovarian cancer can mimic primary ovarian cancers, so imaging methods may be insufficient. The most common non-genital system tumors which metastasize to the ovary are from gastrointestinal system such as; breast, and hematopoietic systems[2].

The structure of the ovary during the intraoperative observation may help for clinic differential diagnosis. The macroscopic presence of bilateral tumor, the implant on the ovarian surface, extra-ovarian mass and solid cystic components may be a predictor of metastatic ovarian tumors. All the bilateral tumors and unilateral tumors smaller than 10 cm are more likely to be metastatic cancer; and the unilateral tumors larger than 10 cm are more likely to have a primary ovarian origin[4].

A mucinous adenocarcinoma of the ovary can be the primary mucinous adenocarcinoma of the ovary or as in our case can originate from other organs or systems which can develop mucinous adenocarcinoma, including particularly the gastrointestinal tract. Histopathological features including infiltrative and nodular invasion pattern, lymphovascular invasion and the presence of signet ring cells can alert for the metastases[4]. In addition, immunohistochemical markers can contribute to determining of the primary origin. However, in the presence of an ovarian tumor with mucinous adenocarcinoma morphology, the similarity in immunohistochemical findings of the primary and metastatic tumors should be kept in mind. Therefore; histopathological features, medical history, clinical and laboratory findings should be evaluated for the discrimination of primary or metastatic tumor. Although there are not any specific tumor markers for cholangiocellular

carcinoma, increased levels of CA 19.9 (>100 U/mL) should be significant for pancreatic and cholangiocellular carcinomas[5]. Despite the fact that the normal appearance of gastro intestinal system and pancreas, increased levels of CA 19.9 (1782.7 U/mL) is remarkable in our case and appropriate with isolated ovarian metastasis. Besides it has been reported that elevated levels of CA 19.9 is correlated with poor prognosis and advanced stage disease[6]. The metastasis rate from the biliary tumors to the ovaries is very low in the current literature[1]. The cases diagnosed with ovarian metastasis before the diagnosis of primary cholangiocellular carcinoma would show much worse prognosis[7]. Whenever synchronous or metachronous metastases progress, identified surgical resection should be always recommended to these patients[8]. In conclusion, metastatic ovarian tumors are a challenging condition for the gynecologists. The difficulties in the differential diagnosis of the metastatic and primary ovarian tumors required a detailed analysis. As many distant organs and tissues may metastasize to the ovaries the patients should be evaluated with medical history, examination of the genital and non-genital system, laboratory findings, as well as intraoperative observation. Prognosis of metastatic ovarian tumors is worse than the primary tumors. Multidisciplinary approach is important in the management of such tumors.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Sefa Kurt, İbrahim Astarcıoğlu, Concept: Sefa Kurt, Çağnur Ulukuş, Design: Sefa Kurt, Çağnur Ulukuş, Data Collection or Processing: Sefa Kurt, Seher Nazlı Kazaz, Analysis or Interpretation: Sefa Kurt, Seher Nazlı Kazaz, Literature Search: Sefa Kurt, Writing: Sefa Kurt.

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References

1. Bhardwaj N, Garcea G, Dennison AR, Maddern GJ. The Surgical Management of Klatskin Tumours: Has Anything Changed in the Last Decade? World J Surg 2015;39:2748-56.
2. Kondi-Pafiti A, Kairi-Vasilatou E, Iavazzo C, Dastamani C, Bakalianou K, Liapis A, et al. Metastatic neoplasms of the ovaries: a clinicopathological study of 97 cases. Arch Gynecol Obstet 2011;284:1283-8.
3. Bayar Ü, Kayar E. Metastatic Ovarian Tumors. Turkiye Klinikleri J Gynecol Obst 2004;14:52-63.
4. Jain V, Gupta K, Kudva R, Rodrigues GS. A case of ovarian metastasis of gall bladder carcinoma simulating primary ovarian neoplasm: diagnostic pitfalls and review of literature. Int J Gynecol Cancer 2006;16 Suppl 1:319-21.
5. Koçak E, Koçak G, Beşir FH, Can M. A case of Klatskin Tumor with High Levels of CA 19-9. Turkiye Klinikleri J Med Sci 2007;27:774-7.
6. Sal V, Demirkiran F, Topuz S, Kahramanoglu I, Yalcin I, Bese T, et al. Surgical Treatment of Metastatic Ovarian Tumors From Extragenital Primary Sites. Int J Gynecol Cancer 2016;26:688-96.
7. Yeshmine F, Hussain M, Dey S, Rahman T, Khatun M. Ovarian Metastases Caused by Cholangiocarcinoma: A rare Krukenberg's Tumor: A Case Study. Bangladesh J of Radiol 2013;21:87-9.
8. Rosa F, Marrelli D, Morgagni P, Cipollari C, Vittimberga G, Framarini M, et al. Krukenberg Tumors of Gastric Origin: The Rationale of Surgical Resection and Perioperative Treatments in a Multicenter Western Experience. World J Surg 2016;40:921-8.

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Angular pregnancy

Açısal gebelik

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Abstract

Angular pregnancy is a rare condition in which the embryo is implanted in the lateral angle of the uterine cavity, medial to the uterotubal junction and round ligament, and causes life-threatening obstetric complications. It is important to differentiate this condition from interstitial and cornual pregnancy because they all result in emergency conditions. Although angular pregnancy can progress to term pregnancy, it may be associated with major obstetric complications such as uterine rupture, placental retention, postpartum hemorrhage, or may need further surgery and hysterectomy. This report describes a case of angular pregnancy from the 6th gestational week and continued until delivery in the 32nd gestational week. Sonographic findings, follow-up, and delivery concerns are described in this manuscript.

Keywords: Angular pregnancy, cornual pregnancy, ectopic pregnancy, antenatal hemorrhage, postpartum hemorrhage

Öz

Açısal gebelik, embriyonun uterin kavitenin lateral açısına, medyal uterotubal bölgeden raund ligamente doğru, yerleşen ve hayatı tehdit eden obstetrik komplikasyondur. İnterstisyel gebelik ve kornual gebelik ayırıcı tanısı önemlidir, çünkü bunların hepsi acil durumla sonuçlanır. Açısal gebelikler term gebeliğe kadar ilerliyebilmesine rağmen, uterin rüptür, plasental retansiyon, postpartum kanama veya histerektomiye kadar gidebilecek cerrahi yöntemlerle sonuçlanabilecek major obstetrik komplikasyonlara yol açabilir. Bu olguda gebeliğin 6. haftasında tanı almış ve 32. haftada doğumuna kadar takip edilmiş açısal gebelik anlatılmıştır. Çalışmamızda ultrasonografi bulguları, takip ve doğum bilgileri anlatılmıştır.

Anahtar Kelimeler: Açısal gebelik, kornual gebelik, ektopik gebelik, antenatal kanama, postpartum kanama

Introduction

Angular pregnancy was first defined in 1898 by the American obstetrician Howard Kelly as implantation of the embryo just medial to the uterotubal junction, in the lateral angle of the uterine cavity[1,2]. Angular pregnancy is distinguished from interstitial pregnancy by embryoposition where lateral uterine enlargement of an angular pregnancy displaces the round ligament upward and outward, whereas interstitial tubal pregnancy is located lateral to the round ligament[1]. No absolute anatomic boundaries distinguish angular pregnancies from normal pregnancies, but the closer the location to the lateral angle of the uterus, the more it may cause visual asymmetry, symptoms, and adverse events when the pregnancy progresses[3].

Angular pregnancy is potentially dangerous and may lead to complications during pregnancy and delivery, such as persistent pelvic pain and bleeding, spontaneous abortion, uterine rupture, retained placenta, placenta accreta, and severe bleeding leading to hysterectomy[1,4,5]. Diagnosis is difficult, many cases may actually go undiagnosed. To the best of our knowledge, no reports have delineated the entire natural course of angular pregnancy from early diagnosis to delivery. We aimed to discuss the possible outcomes of an angular pregnancy and highlight the problems encounered during follow-up.

Case Report

A woman aged 34 years with a prior cesarean delivery, without symptoms, was admitted for a routine first antenatal examination in her 6th gestational week. Endovaginal sonography showed a gestational sac located in the right lateral angle of the uterine cavity. The gestational sac was covered by endometrium of the medial aspect of the uterotubal junction, and the endometrial thickness was continuous with central endometrial lining (Figure 1A, B, C). We informed the patient about possible the diagnoses, natural courses, and complications. After discussing the risks, the patient requested to continue the pregnancy and close follow-up was decided. She presented with slight but

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disturbing abdominal pain and intermittent vaginal bleeding at 9 weeks. Sonography revealed a gestational sac in the right uterine angle, which was continuing to grow towards the cavity (Figure 1D). However, the uterine growth was asymmetrical. Vaginal spotting resolved after 2 weeks. The pregnancy's development towards the uterine cavity continued, the base of the placenta was located in the right uterine angle (Figure 2A). The patient was admitted to the hospital at 27 weeks' gestation because of vaginal bleeding and mild uterine contractions. Sonography revealed a 9x4 cm subcorionic hematoma, anterior and next to the edge of the placenta (Figure 2B). There was no placental abruption. Tocolysis was initiated and antenatal corticosteroid was given because the fetus was immature. The hematoma areas were stabilized aboutfor 5 weeks.

Intermittent vaginal bleeding continued. Fetal biometry continued to progress appropriate to the gestational week. A cesarean section was performed at 32 weeks of gestation because of uterine contractions and dilatation of the cervix. A 1650-g female fetus was delivered. The uterus was seen asymetrically enlarged, the right uterine angle region was bulging. Upon exteriorizing the uterus, a 9x9 cm sacculation was seen (Figure 2C, D). The vessels were excessive and the area was bluishly discolored due to the placental location. The placenta was delivered manually and with difficulty. This area was very thin and lacking myometrial tissue, as confirmed by intrauterine and extrauterine palpation. Due to the continuation of bleeding, 3 square compression sutures with absorbable 0 poliglecaprone were placed passing anterior to the posterior uterine wall where the bleeding was intense. Myometrial contraction was accomplished. Obliteration of this saccular area was confirmed through intrauterine digital examination. The surgery was completed without any further complications. Bleeding was not observed, and the patient was discharged after 72 h.

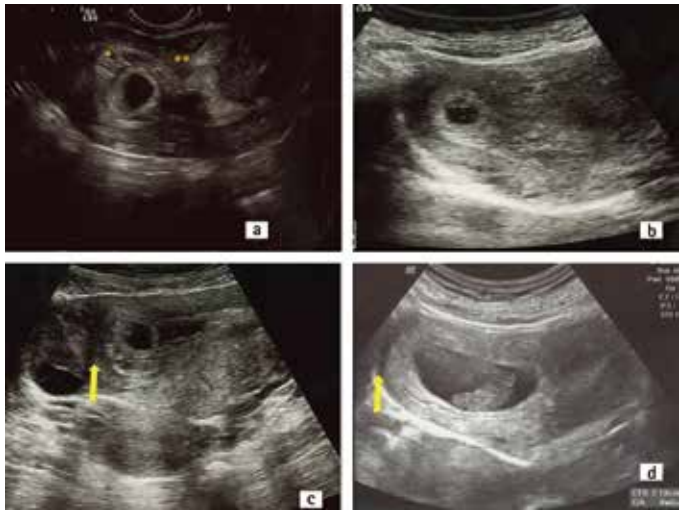

Figure 1. A) Transvaginal ultrasound view of the gestation sac at 6 weeks' gestation. The sac is covered by the endometrium (*) and continuous with the intracavitary endometrial lining (**), B) Transabdominal ultrasound image of the angular pregnancy at 6 weeks' gestation. The gestational sac is located in the right lateral side of the uterus. The myometrium surrounding the sac is thick and the uterus is asymmetric C) The gestastional sac growing towards the cavity at the 7th week, the ovary is seen lateral to the arrow. Note the thickness of the myometrium around the sac. D) Transabdominal ultrasound image of the angular pregnancy at 8+6 weeks' gestation. The asymmetric uterine enlargement is distinct

Discussion

Angular pregnancy is a rare and life-threatening obstetric complication in which the embryo is implanted in the lateral angle of the uterine cavity medial to the uterotubal junction and round ligament[1]. Contrary to interstistial pregnancy, which locate in the muscular layer of the origin of tuba uterina and surrounded by myometrial layer, in angular pregnancy the embryo locates in the lateral wall endometrial thickness of the uterus[6,7]. The surrounding endometrial tissue of embryo is continuous with the intracavitary endometrial line. A strict distinction between these three conditions is clinically important, because their findings, management, and outcomes are different[7]. Interstitial pregnancy may progress without symptoms until inevitable rupture occurs at 12-16 weeks[6,7]. Cornual pregnancy refers to a pregnancy in a rudimentary horn of a septate or bicornuate uterus[6]. In angular pregnancy, the embryo may abort or develop in the uterine cavity[1]. In contrast to interstitial pregnancy, angular pregnancy can progress to term[1,4]. If a patient presents at an advanced gestational age, the physician should suspect angular pregnancy if thickened placenta is located in an asymmetrically confined area of the uterine angle[3]. In the second and third trimester, the placenta

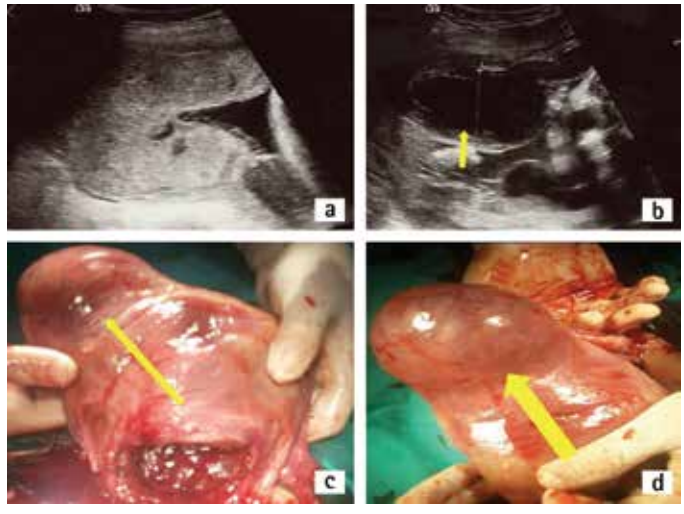

Figure 2. A) At 26 weeks' gestational age, sonogram revealed a thickened and confined placenta at the right uterine angle B) Subchorionic hematoma at the placental edge C) Photograph of the angular pregnancy, anterior view of the uterus. The right cornual area protrudes as a sacculation. The uterus is distinctly asymetric D) The view of the posterior and right lateral side of the uterus. The area is discolored due to excessive vessel formation

may be seen limited to the uterine angle. Contrary to the normal placental growth pattern, the placenta of angular pregnancy must adopt a rigid uterine angle shape. In our opinion, the asymmetric appearance of the uterus, non-vertex fetal presentation, thickened placenta, placental adhesion anomalies, and muscular weakness of the area resulting from placental growth in the restricted, rather sharp edges of the uterine angle. This asymmetry can be seen and palpated in a thin patient in an abdominal examination. It is difficult to diagnose an angular pregnancy with certainty and to differentiate them from other abnormal implantations using ultrasound, because the main anatomic landmark (round ligament) is not visualized with this technique[6]. However, angular pregnancy can be accurately diagnosed with endovaginal sonography, especially during early gestational weeks. Alternatively, 3-D ultrasound and magnetic resonance exams can facilitate diagnosis, reduce the possibility of diagnosis failure, evaluate placenta implantation anomalies, and predict the risk of uterine rupture[3,4,6,8]. However, when magnetic resonance is not available, we believe that the most useful approach for an exact diagnosis is sequential ultrasound evaluations to determine whether the gestational growth is towards the uterine cavity. Angular pregnancies either terminate spontaneously or proceed to term. Even spontaneous termination might be complicated by improper separation of the placenta. A full-term delivery is likely if the gestational sac descends into the uterine cavity[1,4]. Jansen and Elliott[1] reviewed 39 cases of suspected angular pregnancies and reported that 38.5% (10 of 26) had spontaneous or missed abortions, and 13.6% (3 of 22) had uterine ruptures. Recurrent bleeding can continue throughout pregnacy. The increased risk of preterm delivery, placental abruption, growth restriction, and postpartum endometritis is associated with angular pregnancy[3,8]. Abnormal fetal position can be seen, as our case was always in the breech presentation. Potential disadvantages of expectant management may include catastrophic complications such as uterine rupture. This management can be chosen by patient decision. It is necessary to counsel patients about the possible complications and close monitoring and frequent ultrasound examination should be conducted. What complicates the decision for expectant management is that there are no early sonographic signs to establish prognostic factors, although the risk of adverse outcomes can be expected to be higher when the degree of asymmetry of the protrusion at the angle is high, and the myometrium of the uterine angle is thin. It may be safer to terminate these pregnancies during the early stages. However, an inaccessible position of implantation may cause difficult curettage. Hysteroscopy and/or laparoscopy guided curettage, and treatment with methotrexate in early angular pregnancies are the preferred methods of treatment[8].

The site of angular pregnancy could cause uterine atony during delivery due to weakness or lack of myometrial tissue and inadequate contraction, and excessive vascular development. There may even be a need for hysterectomy if accompanied by a placental adhesion anomaly. In a case of suspected retained placenta, despite manual intervention, a coronal incision can be made into the myometrium overlying the placenta. In case of excessive bleeding due to atony, a few square sutures using long absorbable sutures from anterior to posterior through the uterus in order to obliterate the asymmetrical uterine sacculation can be peformed successfully as we did in our case.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İbrahim Alanbay, Mustafa Öztürk, Kazım Emre Karaşahin, Müfit Cemal Yenen, Concept: İbrahim Alanbay, Mustafa Öztürk, Design: İbrahim Alanbay, Mustafa Öztürk, Data Collection or Processing: İbrahim Alanbay, Analysis or Interpretation: İbrahim Alanbay, Literature Search: İbrahim Alanbay, Mustafa Öztürk, Kazım Emre Karaşahin, Writing: İbrahim Alanbay, Mustafa Öztürk, Kazım Emre Karaşahin.

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References

1. Jansen RP, Elliott PM. Angular intrauterine pregnancy. Obstet Gynecol 1981;58:167-75.
2. HA K. Operative Gynecology. Vol II. New York, Appleton; 1898;448-9.
3. Kwon JY, Hwang SJ, Shin JE, Yoon WS, Shin JC, Park IY. Two cases of angular pregnancy complicated by preterm labor and placental abruption at mid-pregnancy. J Obstet Gynaecol Res 2011;37:958-62.
4. Alves JA, Alves NG, Alencar Junior CA, Feitosa FE, da Silva Costa F. Term angular pregnancy: successful expectant management. J Obstet Gynaecol Res 2011;37:641-4.
5. Shekhar S, Verma S, Motey R, Kaushal R. Hysterotomy for retained placenta with imminent uterine rupture in a preterm angular pregnancy. Acta Obstet Gynecol Scand 2010;89:1615-6.
6. Moawad NS, Mahajan ST, Moniz MH, Taylor SE, Hurd WW. Current diagnosis and treatment of interstitial pregnancy. Am J Obstet Gynecol 2010;202:15-29.
7. Arleo EK, DeFilippis EM. Cornual, interstitial, and angular pregnancies: clarifying the terms and a review of the literature. Clin Imaging 2014;38:763-70.
8. Tarim E, Ulusan S, Kilicdag E, Yildirim T, Bagis T, Kuscu E. Angular pregnancy. J Obstet Gynaecol Res 2004;30:377-9.

Case Report / Olgu Sunumu

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Severe methotrexate toxicity after treatment for ectopic pregnancy: A case report

Ektopik gebelik tedavisi sonrası ağır metotreksat toksisitesi: Olgu sunumu

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Abstract

Severe methotrexate toxicity due to medical treatment of an ectopic pregnancy is presented. The feasibility of low-dose use and success of methotrexate makes it the first drug in the medical treatment of ectopic pregnancies. Besides its advantages, it should be used with caution and severe toxicity should be kept in mind.

Keywords: Methotrexate, pregnancy, ectopic, toxicity

Öz

Bir ektopik gebelik olgusunun medikal tedavisi sonrası ağır metotreksat toksisitesi sunulmaktadır. Düşük dozda kullanılması, kolay kullanımı ve başarısı, metotreksatı ektopik gebelik olgularının medikal tedavisinde ilk seçenek ilaç yapmaktadır. Avantajları yanında kullanımı esnasında ağır toksisite akılda tutularak dikkatle kullanılmalıdır.

Anahtar Kelimeler: Metotreksat, gebelik, ektopik, toksisite

Introduction

Ectopic pregnancy is a serious condition in gynecologic practice. Treatment options for ectopic pregnancy include surgical treatment, expectant management, and medical treatment. Methotrexate (MTX) treatment is preferred for its fewer adverse effects and cost effectiveness[1].

MTX is a folic acid antagonist and is generally used for the treatment of malignancies, autoimmune diseases, and ectopic pregnancies[2]. The inhibitory effect on DNA synthesis of MTX is the rationale in the treatment of ectopic pregnancy in which the target is trophoblasts and fetal cells. Ninety percent of MTX given intravenously undergoes renal excretion without any change within 24 hours[3]. Low-dose use of MTX gives freedom to a physician to use it frequently in the treatment of ectopic pregnancies. MTX treatment has two protocols; single dose and multiple dose regimens. The single injection of the drug, less follow-up time, lower cost, and no requirement for folinic acid use makes the single-dose protocol the most preferred. MTX is given 50 mg/m^2 intramuscularly. Levels of beta-human chorionic gonadotropin (β-hCG) are measured on the 4th and 7th day of treatment. A second dose is not needed if the decrease in β-hCG levels is more than 15% between days 4 and 7. A second dose of MTX is needed in 15-20% of cases and only 1% of women who receive the single-dose protocol require a third dose[4-6]. Adverse effects are generally mild and self-limited; the most common are stomatitis and conjunctivitis. Rare adverse effects include gastritis, enteritis, dermatitis, pneumonitis, alopecia, elevated liver enzymes, and bone marrow suppression. Approximately 30 percent of patients on the single-dose protocol have adverse effects; this rate is lower for patients on multi-dose regimens (40%)[7].

Renal and hepatic diseases, immunodeficiency, active pulmonary disease, and peptic ulcer disease are contraindications for MTX treatment[8-10]. Herein, an otherwise healthy woman who had a severe adverse event with low-dose MTX treatment is presented.

Case Report

A gravida 3 woman aged 38 years was admitted to our hospital with symptoms of pelvic pain, diarrhea, and oral lesions. She had MTX (50 mg/m^2) treatment when her β-hCG level was

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2279 mIU/mL. Seven days after the first dose, a second dose of MTX treatment was given due to elevated β-hCG (2304 mIU/mL) and an ultrasound finding of a 2-cm gestational sac in the right fallopian tube. On day 4 of the second dose, emergency laparoscopic salpingectomy was performed for tubal rupture with hemorrhage. She was discharged from hospital on the first postoperative day and readmitted on the second day with bloody diarrhea (ten times a day), oral lesions, and macular rush on the scalp, neck, and chest regions. No remarkable details were noted in her medical history except MTX treatment. In the physical examination, she was pale and her vital signs and body temperature were in the normal range, and a macular rash on the chest, neck and scalp area (Figure 1) and mucositis in oral mucosa were detected (Figure 2). A blood count revealed hemoglobin (Hb) level of 6.4 gr/dL, the white blood cells number was 2000 /μL, creatinine was 1.76 mg/dL, β-hcg level was 91 mIu/mL. During the clinical follow-up, the general condition of the patient deteriorated. On the same day, her Hb level was 6.2 gr/dL and the white blood cell number was 1600/μL (Table 1). Lesions in the oral mucosa and skin increased and the diarrhea worsened. She was transferred to the intensive care unit. The serum level of MTX was high (more than 2 picograms/L). Calcium folinate infusion, and erythrocyte (4 units), thrombocyte (6 units) replacement and intravenous hydration and nutrition, and broad spectrum antibiotics were started. Sodium bicarbonate was administered via intravenous infusion to increase the excretion of the MTX alkalization of urine. Despite the supplementary treatment and folinic acid treatment, high levels of MTX continued and her cytopenic clinical state worsened. Plasmapheresis was considered for lowering MTX levels because glucarpidase (carboxypeptidase G2) is not available in Turkey. The level of MTX decreased after performing plasmapheresis. The patient's symptoms and clinical findings regressed. After 18 days of hospitalization (one week intensive care unit) she was discharged from hospital with no symptoms.

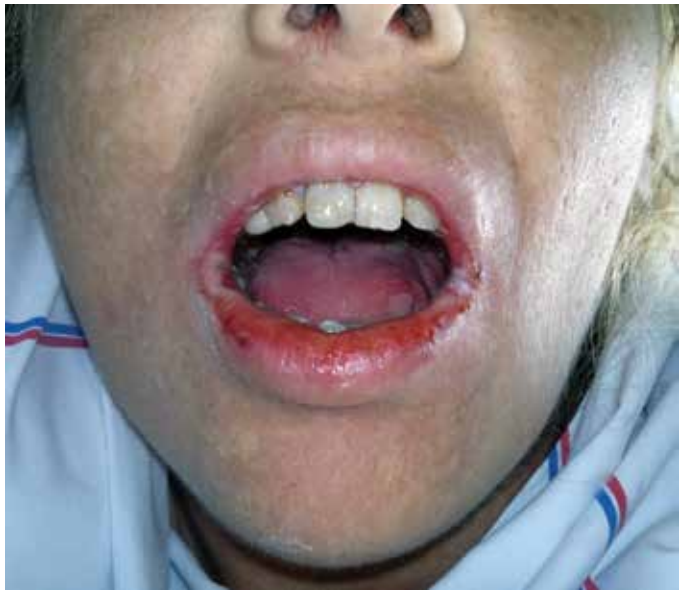

Figure 1. Macular rash on the chest and neck area

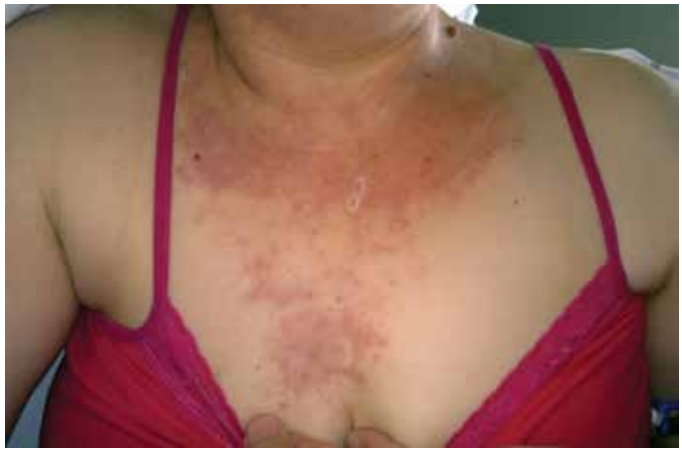

Figure 2. Oral lesions and mucositis detected

Discussion

MTX is a cheap and minimally toxic drug in low doses and is widely used in patients with non-ruptured ectopic pregnancy in suitable clinical conditions. Before treatment with MTX, a viable intrauterine pregnancy must be excluded; β-hCG levels, renal and liver function tests, and a complete blood count should be checked. MTX treatment has single-dose and multiple-dose protocols. Adverse effects can be seen more frequently in multi-dose protocols[7]. The adverse effects of MTX are caused by irreversible inhibition of the enzyme dihydrofolate reductase in purine synthesis. Decreases in blood cells and hemorrhage from the gastrointestinal tract are due to the effect on rapidly dividing cells of the bone marrow and intestinal tract[11]. Severe adverse effects are infrequent in MTX treatment for ectopic pregnancy. The potential severe adverse effects of MTX treatment are hepatotoxicity, pulmonary toxicity, risk of infection, myelosupression, and nephrotoxicity. Hepatotoxicity results from direct damage to hepatocytes or in patients with concomitant viral hepatitis. Minor aminotransferase elevations

Table 1. Complete blood count values

	Hb (gr/dL)	WBC (/μL)	PLT (/μL)
Admission day	6.4	2000	104000
Admission day	6.2	1600	106000
1st day	7.3	1800	105000
1st day	7.8	1200	91000
2nd day	7.7	700	65000
3rd day	7.1	500	47000
4th day	6.7	300	37000
10th day	9.6	24000	91000

Hb: Hemoglobin, WBC: White blood cells, PLT: Platelet

are common but hepatic steatosis, fibrosis, and cirrhosis are seen rarely. For this reason, screening for hepatitis B and hepatitis C virus infection and hepatic enzymes should be performed before initial therapy. MTX is an immunomodulatory but not significantly immunosuppressive agent. Myelosuppression is the major dose-limiting adverse effect of high- dose MTX, but it is infrequent in low-dose therapy. Hematologic toxicity associated with macrocytic red blood cells may be seen, but a more serious abnormality is the development of pancytopenia[12]. Therefore, guidelines from the American College of Rheumatology recommend that a routine peripheral complete blood should be performed every four weeks in rheumatoid arthritis treatment[13]. Nephrotoxicity due to MTX rarely occurs in treatment with high doses. A slight decrease in creatinine clearance can be seen even at low, weekly doses used in rheumatoid diseases[14]. Development of myelosuppression and mucositis such as MTX- related toxicity risk, is highest in patients with prolonged exposure to high levels of plasma MTX concentrations. Glucarpidase, a bacterial enzyme, is used for a rapid decrease of plasma MTX levels, which hydrolyses MTX to its inactive metabolites. The greatest benefit is achieved with glucarpidase when plasma MTX concentrations are high[15]. Low-dose MTX is used in the medical treatment of ectopic pregnancy. Severe toxicity is an unexpected condition. In the present case, two doses of MTX were given one week apart but severe toxicity occurred. Compared with other treatment indications of MTX, the dose was very low but the subsequent adverse effects were detrimental and life threatening. Although the patient had no renal insufficiency, a high serum level of MTX was detected. Intensive care unit treatment and folinic acid replacement failed. Fortunately, the patient's signs and symptoms regressed with plasmapheresis. In review of the literature, severe toxicity due to MTX treatment for ectopic pregnancy was reported in a patient with renal insufficiency but severe toxicity in a healthy woman has not been reported[2]. In conclusion, unexpected toxicity with MTX should be kept in mind during use of this simple treatment.

Ethics

Informed Consent: Consent form was filled out by participant.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Mehmet Vural, Sunullah Soysal, Concept: Mehmet Vural, Sunullah Soysal, Design: Begüm Yıldızhan, Mehmet Vural, Data Collection or Processing: Sunullah Soysal, Gökçe Anık İlhan, Analysis or Interpretation: Begüm Yıldızhan, Gökçe Anık İlhan, Literature Search: Sunullah Soysal, Gökçe Anık İlhan, Writing: Sunullah Soysal.
Conflict of Interest: No conflict of interest was declared by the authors.

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References

1. Cohen A, Zakar L, Gil Y, Amer-Alshiek J, Bibi G, Almog B, et al. Methotrexate success rates in progressing ectopic pregnancies: a reappraisal. Am J Obstet Gynecol 2014;211:128 e1-5.
2. Willner N, Storch S, Tadmor T, Schiff E. Almost a tragedy: severe methotrexate toxicity in a hemodialysis patient treated for ectopic pregnancy. Eur J Clin Pharmacol 2014;70:261-3.
3. Bleyer WA. The clinical pharmacology of methotrexate: new applications of an old drug. Cancer 1978;41:36-51.
4. Barnhart KT, Gosman G, Ashby R, Sammel M. The medical management of ectopic pregnancy: a meta-analysis comparing "single dose" and "multidose" regimens. Obstet Gynecol 2003;101:778-84.
5. Guvendag Guven ES, Dilbaz S, Dilbaz B, Aykan Yildirim B, Akdag D, Haberal A. Comparison of single and multiple dose methotrexate therapy for unruptured tubal ectopic pregnancy: a prospective randomized study. Acta Obstet Gynecol Scand 2010;89:889-95.
6. Lipscomb GH, Bran D, McCord ML, Portera JC, Ling FW. Analysis of three hundred fifteen ectopic pregnancies treated with single-dose methotrexate. Am J Obstet Gynecol 1998;178:1354-8.
7. Barnhart KT, Gosman G, Ashby R, Sammel M. The medical management of ectopic pregnancy: a meta-analysis comparing "single dose" and "multidose" regimens. Obstet Gynecol 2003;101:778-84.
8. Kelly H, Harvey D, Moll S. A cautionary tale: fatal outcome of methotrexate therapy given for management of ectopic pregnancy. Obstet Gynecol 2006;107:439-41.
9. Teal SB. A cautionary tale: fatal outcome of methotrexate therapy given for management of ectopic pregnancy. Obstet Gynecol 2006;107:1420-1; author reply 1.
10. Willner N, Storch S, Tadmor T, Schiff E. Almost a tragedy: severe methotrexate toxicity in a hemodialysis patient treated for ectopic pregnancy. Eur J Clin Pharmacol 2014;70:261-3.
11. Calabresi P, Chabner BA. Antineoplastic agents, chapter 52. In: Gilman A, Goodman LS, Goodman A editors. The pharmacological basis of therapeutics. 8th ed. New York: Macmillan; 1990. p. 1275-6.
12. Gutierrez-Urena S, Molina JF, Garcia CO, Cuellar ML, Espinoza LR. Pancytopenia secondary to methotrexate therapy in rheumatoid arthritis. Arthritis Rheum 1996;39:272-6.
13. Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum 2008;59:762-84.
14. Kremer JM, Petrillo GF, Hamilton RA. Pharmacokinetics and renal function in patients with rheumatoid arthritis receiving a standard dose of oral weekly methotrexate: association with significant decreases in creatinine clearance and renal clearance of the drug after 6 months of therapy. J Rheumatol 1995;22:38-40.
15. Schwartz S, Borner K, Muller K, Martus P, Fischer L, Korfel A, et al. Glucarpidase (carboxypeptidase g2) intervention in adult and elderly cancer patients with renal dysfunction and delayed methotrexate elimination after high-dose methotrexate therapy. Oncologist 2007;12:1299-308.

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