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Clinical Investigations

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galenos yayınevi

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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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A separate title page should list;

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- 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).

Precis

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."]).

· Materials 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.

Keywords

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

Turkish abstracts should have keywords "Anahtar Kelimeler" picked from www.atifdizini.com under "Türkiye Bilim Terimleri" link.

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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.

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.

Materials 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

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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.

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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:

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TURKISH JOURNAL OF OBSTETRICS AND GYNECOLOGY

LETTER FROM THE PRESIDENT

Dear Colleagues,

First of all, we would like to wish you all a very happy, healthy, prosperous new year ahead.

In 2019, we hope that it would be a wonderful new year filled with success, happiness, devotion, commitment among obstetricians and gynecologist. Since we are dealing with severe problems such as violation leading to the courts, we hope that it would be a year of attachment and collaboration. We invite all our collagues to support each other and to stand together in order to overcome the aforementioned issues and to work in peace and joy.

While welcoming the new year, we are grateful for our work in 2018. We especially thank the editorial board, all board members, authors, worlwide readers for their great work and efforts in making our journal a success.

In 2019, we believe that we will continue to grow and achieve; therefore, we look forward to your valuable work and contributions.

We hope that 2019 would be year of collaboration and devotion for our community.

Sincerely,

Ateş Karateke, Prof. M.D.
President of TSOG

TURKISH JOURNAL OF OBSTETRICS AND GYNECOLOGY

EDITORIAL

Dear Colleagues,

2018 has been a busy year for our journal and for our society. We have conducted many courses on "How to write a manuscript?". It is nice to see an increasing participation in our courses conducted in conjunction with our society "Turkish Society of Obstetrics and Gynecology". It is nice to see that the quality of studies submitted for publication in our journal is increasing. This increase in submiss, on demands an increase in work hours and we need more refrees and experts to evaluate the submitted studies. Accordingly a new editorial board with more refrees will be at your service in 2019.

Our journal has passed 12000 views per month with more than 10000 full text views and about 1500 pdf downloads of the fulltexts. We hope this will cause an increase in citation index of our journal. This success story is a combined victory of all contributors to our journal. Thank you for letting us have the oppurtunity to evaluate your work and thanks to all refrees and editorial board for donating their time and knowledge fort he journal.

I wish you all the best in 2019, and wish a year with more scientific discoveries.

Eray Çalışkan
Editor in Chief

Clinical Investigation / Araştırma

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Turk J Obstet Gynecol 2018;15:210-6

Pelvic floor disorders associated with higher-level sexual dysfunction in the Kersa district, Ethiopia

Etiyopya Kersa bölgesinde yüksek düzeyde cinsel işlev bozukluğu ile ilişkili pelvik taban bozuklukları

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Abstract

Objective: To assess the prevalence of female sexual dysfunction and its association with pelvic floor disorder (PFD) in a large scale, community-based study.

Materials and Methods: A total of 2389 women who were married and still in union at the time of the study were drawn from 3432 women who had ever been married who participated in a PFD study. Study participants were selected through a multistage sampling procedure based on Kersa Health and Demographic Surveillance System database. The Female Sexual Function Index questionnaire was employed to collect data. The index score <26.55 was used as a cut-off point for sexual dysfunction. The content of the tool was validated and internal reliability was checked using Cronbach's alpha. Poisson regression model with robust variance estimation was used to investigate the relationship between PFDs and sexual dysfunction.

Results: From the total 2389 participants, 1127 [47.0%; 95% confidence interval (CI): 45.0-49.0] had sexual dysfunction. Sexual desire disorder was the most prevalent disorder (72.0%; 95% CI: 70.0-74.0). After controlling for confounding factors, the prevalence of female sexual dysfunction was found as 56% (adjusted prevalence ratio, 1.56; 95% CI: 1.44-1.69) higher with women with PFD as compared with women without PFD.

Conclusion: In the rural community of Kersa, about half of the women have sexual dysfunction and it is significantly associated with PFD. This would call for an urgent intervention against PFD to maximize the women's sexual and reproductive health.

Keywords: Sexual dysfunction, physiological, pelvic floor diseases, women, Ethiopia

Öz

Amaç: Toplumsal temelli olan bu çalışmada, kadın cinsel işlev bozukluğunun prevalansını ve pelvik taban bozukluğu (PTB) ile ilişkisini geniş çaplı olarak değerlendirmektir.

Gereç ve Yöntemler: Çalışma sırasında, evli ve hala birliktelik gösteren toplam 2389 kadın, evli olan ve bir PTB çalışmasına katılan 3432 kadın arasından araştırmaya alınmıştır. Çalışma katılımcıları, Kersa Sağlık ve Demografik Denetim Sistemi veri tabanına dayalı çok aşamalı bir örnekleme prosedürü ile seçilmiştir. Verileri toplamak için Kadın Cinsel İşlev İndeksi anketi kullanılmıştır. İndeks skoru (<26,55), cinsel işlev bozukluğu için sınır noktası olarak değerlendirilmiştir. Aracın içeriği doğrulanmış ve iç güvenilirlik Cronbach alfa kullanılarak kontrol edilmiştir. PTB'ler ve cinsel işlev bozukluğu arasındaki ilişkiyi araştırmak için sağlam varyans tahminine sahip Poisson regresyon modeli kullanılmıştır.

Bulgular: Toplam 2389 katılımcının 1127'sinde [%47; %95 güven aralığı (GA): 45,0-49,0] cinsel işlev bozukluğu mevcuttu. Cinsel istek bozukluğu en sık görülen rahatsızlık idi (%72,0; %95 GA: 70,0-74,0). Karıştırıcı faktörler kontrol edildikten sonra, kadın cinsel işlev bozukluğu prevalansı, PTB'si olmayan kadınlarla karşılaştırıldığında, PTB'li kadınlarda %56 (düzeltilmiş prevalans oranı, 1,56; %95 GA: 1,44-1,69) daha yüksek bulundu.

Sonuç: Kersa'nın kırsal toplumunda, kadınların yaklaşık yarısı cinsel işlev bozukluğuna sahiptir ve bu durum önemli derecede PTB ile ilişkilidir. Bu, kadınların cinsel ve üreme sağlığını en üst seviyeye çıkarmak için PTB'ye karşı acil bir müdahale çağrısıdır.

Anahtar Kelimeler: Cinsel işlev bozukluğu, fizyolojik, pelvik taban bozukluğu, kadınlar, Etiyopya

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PRECIS: Using Female Sexual Function Index questionnaire, 47% of participants were identified having sexual dysfunction, and sexual dysfunction was 56% higher with women with pelvic floor disorder as compared to women without pelvic floor disorder.

Introduction

Sexual dysfunction is a heterogeneous group of disorders characterized by a clinically significant disturbance in a person's ability to respond sexually or to experience sexual pleasure[1]. Sexual dysfunction comprises physical, social, and psychological dimensions of disturbance. It can affect any phase of sexual functioning including desire, arousal, orgasm, satisfaction, lubrication, and pain[2]. Sexual dysfunction has detrimental impacts on women's quality of life, mainly on their interpersonal relationships, ability of reproduction, and psychological well-being[3,4].

Globally, 41% of women have sexual dysfunction. This problem is more prevalent among African women (62%) [5]. Viewing sex as a method of procreation (in contrast to pleasure), genital mutilation, gender inequality, and poor reproductive health conditions fuel the burden of female sexual dysfunction (FSD) in developing regions[5-7].

Pelvic floor disorders (PFDs), whose symptoms involve urinary incontinence, over-active bladder (OAB), pelvic organ prolapse (POP), and fecal incontinence, can adversely affect the sexual function and satisfaction of women[8]. Women with PFD fail to attain sexual function due to discomfort, mechanical obstruction of prolapsed organ, pain, and leakage. For these reasons and due to the fear of incontinence[9], they avoid sexual intercourse or restrict sexual activity. In addition to its physical effect, PFD causes women to develop low self-esteem, negative self-image especially about their body, and depression. It is generally believed that all these directly affect the women's relationship with their partner and aggravate in them sexual dysfunctions[10,11]. Yet, the available research findings on the relationship between PFD and sexual function remains indeterminate, and, in many cases, contradicting. Some studies report that sexual dysfunction makes little or no difference between women with and without PFD[12,13]. Whereas in other studies, PFD relates to FSD in bivariate analysis, but loses its relation when adjusted for other variables[13,14]. Furthermore, other studies quite intriguingly show that PFD is significantly associated with sexual dysfunction[4,15].

Added to the aforementioned contradictory and indeterminate stories, in developing countries such as Ethiopia, sexual behaviors, activities, and problems are not discussed openly. To discuss these is considered an utter social taboo when it comes to women, particularly in the Ethiopian context. Partly due to this, the prevalence and burden of FSD remains largely less studied or unknown. Therefore, this study attempts to assess the prevalence of sexual dysfunction as well as examine the relationship between PFD and sexual dysfunction among women with and without PFD in Eastern Ethiopia.

Materials and Methods

This study is part of a larger community-based cross-sectional study, which was established to investigate factors associated with PFDs. The study selected the Kersa Health and Demography Surveillance System (HDSS), Kersa District, Ethiopia, as its setting. The study was conducted from August 10th, to September 4th, 2016.

From among 3432 women who had ever been married participating in the PFD study, 2389 women who were married and still in union at the time of the study were selected. At the time of study, they had been residing inside Kersa HDSS for at least six months. A multi-stage, stratified, random sampling procedure proportional to the size of the household in each kebeles (small administrative unit in Ethiopia) was used to enroll the study participants. The Kersa HDSS database was used as a sampling frame. The study was approved by Haramaya University Health and Medical Sciences College Institutional Health Research ethics review committee (approval number: IHRERC/001/2016). Consent form was filled out by all participants.

Data collection tools

A standardized Female Sexual Function Index (FSFI) questionnaire was adopted and distributed in order to measure sexual function[2,16]. A PFD questionnaire was customized and adapted from the literature[17]. The socio-demographic and obstetric conditions of the participants were also collected using a structured questionnaire adopted form a national survey document[18]. The contents of the questionnaires were validated by three gynecologists and two reproductive health experts. Further, the questionnaires were pre-tested in a similar setting and refined. This was done to enhance the appropriateness and fitness of the tools to the social and cultural norms. Experienced female data collectors and field supervisors fluent in the local languages were recruited and trained for four days before the fieldwork. The training included field procedures, interviewing techniques, and discussion on the content of the tools. Field supervisors checked compliance to field procedures and the completeness of the questionnaires in the field. The data collectors undertook interviews with the participants in private settings in the interviewees' homes.

The study protocol was approved by Haramaya University Health and Medical Sciences College Institutional Health Research Ethics Review Committee. Written informed consent was obtained from each participant. In order to protect the confidentiality of the information, names and identification were not included in the written questionnaires.

Measurement

Sexual function, the outcome variable for this study, was evaluated using the FSFI questionnaire, which is a 19-item inventory measuring sexual function over a 4-week period in six domains. The domains include desire (items 1 and 2), arousal (items 3-6), lubrication (items 7-10), orgasm (items 11-13), satisfaction (items 14-16), and pain (items 17-19). The response format of four of the items is a 5-point Likert scale. Other items are scored on a scale from 0 to 5, with zero score representing "no sexual activity". Ratings of 1 to 5 indicate level of sexual functioning (e.g., 1: extremely difficult, 2: very difficult, 3: difficult, 4: slightly difficult, 5: not difficult)[16]. By adding the scores of the individual items that comprise the domain and multiplying the sum by domain factor, individual domain scores were obtained. Then, the total sexual function score was obtained by adding the six domain scores. The full-scale score range is from 2.0 to 36.0 with higher scores indicating better function. Women with total FSFI scores less than 26.55 were classified as having sexual dysfunction[2,16]. Sexual function of each domain was categorized based on a cut-off point provided in the literature[2]. Thus, the outcome variable was dichotomized into having sexual dysfunction or not. We checked the internal consistency of the FSFI in this study setting; the FSFI scale had good psychometric properties, with high internal consistency (Cronbach's alpha values between 0.85 and 0.94). The independent variables includd PFDs, obstetrics history, and socio-demographic characteristics. PFD was assessed using an interviewer-administered questionnaire. The questionnaire was customized and adapted from the literature[17]. Each PFD [stress urinary incontinence (SUI), OAB, POP, and anal incontinence] was dichotomized as present or absent based on the responses to each symptom domain. PFDs were dichotomized as women with or without PFD. The detail of this section has been described in detail elsewhere[19]. Obstetrics history was coded as follows: parity was coded in para 1-4 and para 5 and above; history of abortion was coded as "yes" or "no"; age at first child birth was categorized into less than 18 and 18-and-above years; age at first marriage was grouped into 10-14, 15-19, and 20-and-above years.

Statistical Analysis

The obtained data were double-entered into Epi-Data 3.1 and validated using the same statistical software. Then, the data were analyzed using STATA version 14. The overall prevalence of sexual dysfunction with in all domains was obtained with 95% confidence intervals (CI). The proportion of sexual dysfunction among women with PFD was also obtained with 95% CI. When the outcome of interest was common (more than 10%), the odds ratio overestimated the prevalence ratio (PR) and logistic regression model produced poor estimates[20]. Hence, the Poisson regression analysis model was employed with robust variance estimation in order to investigate the relationship between PFD and sexual function. Bivariate analysis was first made and the variables with a p value less than 0.2 were included to the subsequent model building. Model 1 was built to examine the association of socio-demographic and personal behaviors with FSD. Subsequently, relevant obstetrics history variables were included into model 2 to assess their relationship with FSD when controlling for socio-demographic and personal behaviors. The final model (model 3) was built using PFD variables and all variables in model 1 and model 2 were employed to assess the relationship between PFD and FSD. These were reported in an adjusted PR (APR) with 95% CI. Multi-collinearity was assessed using variance inflation factors. Interaction was also checked among the independent variables.

Results

The mean age [± standard deviation] of the participants was 32±10 years. The mean gravidity was 5±3 and the mean parity was 5±2. The majority (74%) of the participants did not attend school and 65% reported that they consumed Khat (*Catha edulis*), a stimulant leaf commonly consumed in the study area. Ten percent of the participants had married more than once. Eighteen percent had at least one type of PFD (Table 1). Forty-seven percent (95% CI: 45-49) of the respondents had sexual dysfunction. Sexual desire disorder was the most prevalent form of FSD (72.0%; 95% CI: 70-74), followed by arousal disorder (52%; 95% CI: 50-54), and pain disorder, the least being 5.0% (95% CI: 4-6) (Figure 1). Among women with sexual dysfunction, 24.0% had only one type of sexual dysfunction, 26.0% had two types, and 4.0% had all six types of sexual dysfunction (Figure 2). The prevalence of desire disorder was 85.0% (95% CI: 81-88) among women with PFD, whereas it was 69.0% (95% CI: 67-71) among women without PFD (Figure 3). Women with PFD were more likely to report sexual dysfunction than women without PFD. Adjusting for other characteristics did not affect the estimation of the association between PFD and sexual dysfunction. Finally, a Poisson regression model was used to adjust for socio-demographic data, personal behaviours, and obstetric variables. Nevertheless, the result showed that PFD maintained its association (APR, 1.56; 95% CI: 1.44-1.69). Moreover, the results indicated that there was a significant relationship between educational level and sexual dysfunction. That is, sexual dysfunction increased by 31% (APR, 1.31; 95% CI: 1.15-1.50) among uneducated women compared with educated women. Also, the result indicated that consuming Khat and grand multi-parity were associated with a 12% and 41% increase in the prevalence of sexual dysfunction (APR, 1.12; 95% CI: 1.02-1.24) and (APR, 1.41; 95% CI: 1.28-1.56), respectively (Table 2).

Table 1. Socio-demographic characteristics and reproductive health history among women in sexual relationships living in Kersa Health and Demography Surveillance System, Ethiopia 2016

Variable	n (%)
Educational level (n=2389)	-
No schooling	1818 (76.1)
Some education	571 (23.9)
Age at first marriage (years) (n=2389)	-
10-14	224 (9.4)
15-19	2002 (83.8)
≥20	163 (6.8)
Married more than once (n=2351)	-
Yes	239 (10.2)
No	2112 (89.8)
Consumed Khat (n=2389)	-
Yes	1546 (64.7)
No	843 (35.3)
Abortion history (n=2314)	-
Yes	363 (15.7)
No	1951 (84.3)
Parity (n=2297)	-
1-4	1049 (45.7)
≥5	1248 (54.3)
Age at first child birth (n=2279)	-
Less than 18	996 (43.7)
≥18	1283 (56.3)
At least one types of PFD (n=2389)	-
Yes	432 (18.1)
No	1957 (81.9)

PFD: Pelvic floor disorder

Discussion

As was illustrated above, 47.0% of the participants in this study had sexual dysfunction. About three-quarters of them had sexual desire disorder, and 1 in 20 had pain disorder. PFD was found to be an independent associated factor for FSD. Our results documented that sexual dysfunction was more prevalent among women with PFDs. In other words, the findings indicate that PFD affects women's reproductive and sexual health. The 47% prevalence of sexual dysfunction in this study is consistent with studies conducted in different parts of the world[5,21,22]. This high prevalence of sexual dysfunction can causes poor quality of life, relationship breakdown and unhappiness that leads to divorce if the

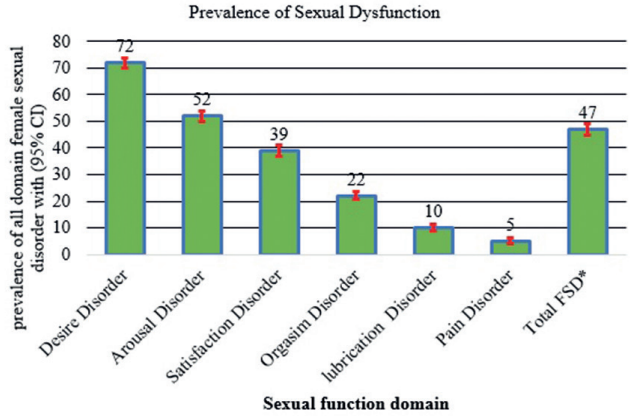

Figure 1. Prevalence of female sexual dysfunction among women living in Kersa Health and Demography Surveillance System, Ethiopia, 2016

*FSD: Female sexual dysfunction, CI: Confidence interval

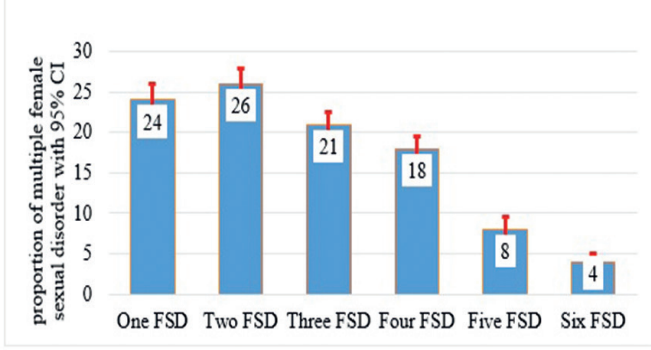

Figure 2. Prevalence of multiple sexual dysfunction among women living in Kersa Health and Demography Surveillance System, Ethiopia, 2016

FSD: Female sexual dysfunction, CI: Confidence interval

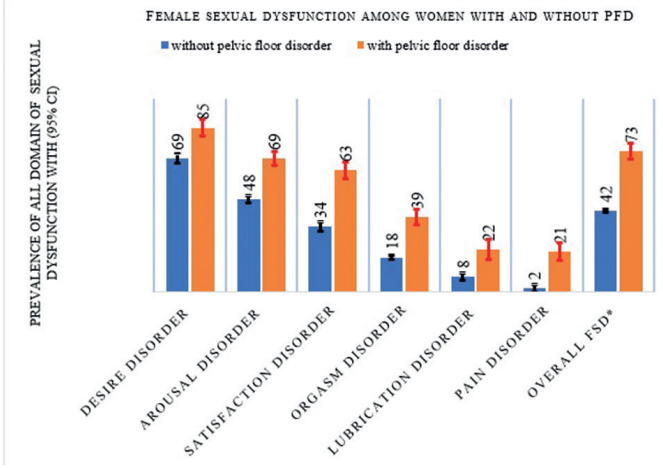

Figure 3. Prevalence of sexual dysfunction among women with and without pelvic floor disorder living in Kersa Health and Demography Surveillance System, Ethiopia, 2016

FSD: Female sexual dysfunction, CI: Confidence interval, PFD: Pelvic floor disorder

Table 2. Factors associated with female sexual dysfunction among ever married women living in Kersa Health and Demography Surveillance System, Ethiopia 2016

Sexual dysfunction (n/N=1127/2389)					
Variable	n (%) of sexual dysfunction	CPR (95% CI) Bivariate model	APR (95% CI) model 1	APR (95% CI) model 2	APR (95% CI) final model
Socio-demographic and personal behaviors					
Age first marriage					
10-14	101 (45.09)	0.87 (0.710-1.07)	0.84 (0.68-1.03)	0.70 (0.56-0.88)	0.72 (0.58-0.89)
15-19	942 (47.05)	0.91 (0.78-1.06)	0.92 (0.79-1.07)	0.83 (0.71-0.97)	0.85 (0.73-0.99)
>20	84 (51.53)	1	1	1	1
Educational status					
No schooling	940 (51.71)	1.578 (1.39-1.79)	1.50 (1.32-1.70)	1.34 (1.17-1.53)	1.31 (1.15-1.50)
Has some education	187 (32.75)	1	1	1	1
Married more than once					
No	976 (46.21)	1	1	1	1
Yes	138 (58.16)	1.25 (1.11-1.41)	1.21 (1.07-1.36)	1.21 (1.08-1.36)	1.18 (1.06-1.33)
Consume Khat					
No	809 (37.72)	1	1	1	1
Yes	315 (52.33)	1.38 (1.25-1.53)	1.30 (1.17-1.43)	1.14 (1.03-1.26)	1.12 (1.02-1.24)
Obstetrics factors parity					
1-4	375 (35.75)	1		1	1
>5	725 (58.09)	1.62 (1.47-1.78)		1.42 (1.28-1.57)	1.41 (1.28-1.56)
Abortion history					
No	890 (45.62)	1		1	1
Yes	218 (60.06)	1.31 (1.19-1.45)		1.18 (1.07-1.30)	1.10 (1.03-1.21)
Age first birth					
less than 18	512 (51.41)	1.13 (1.045-1.24)		1.12 (1.03-1.23)	1.10 (1.01-1.20)
>18	579 (45.13)	1		1	1
Pelvic floor disorder					
PFD					
No	813 (41.54)	1			1
Yes	314 (72.69)	1.74 (1.61-1.89)			1.56 (1.44-1.69)

APR: Adjusted prevalence ratio, CPR: Crude prevalence ratio, CI: Confidence interval, PFD: Pelvic floor disorder

couple are unable to resolve it[8,22,23]. Biopsychosocial factors like female genital mutilation, poor interpersonal relationship with spouse, lack of privacy and uncomfortable surrounding, and cultural taboos that prevent open discussion on sexual issues exacerbate negative sexual functions[5,7,24]. Among the six domains of sexual function, desire disorder (72.0%), and arousal disorder (52.0%) are the most frequently reported symptoms in this study. Pain disorder is the least reported problem with 5%. Desire and arousal are co-occurring event in sexual process and they share a common latent factors[25]. Our finding is consistent with other study's finding[26]. This high prevalence of sexual desire and arousal disorder in this study might be explained by the generic idea that women in traditional societies should not show sexual desire for it is a taboo for women to express or show her sexual desire[6,7,25]. In this study, 39.0% and 22.0% of the women had satisfaction and orgasmic disorders, respectively. A possible explanation for this is that these women experience limited sexual education, lack of awareness on genital anatomy and function, and poor sexual relationship. It is worth nothing, that satisfaction

disorder had a direct link to marital and partner relationship quality[21]. Moreover, in this study, the prevalence of FSD increased by 56.0% among women with PFD compared to women without PFD, a finding which is consistent with other studies[4,27,28]. Pelvic floor function has a direct role in maintaining genital arousal and orgasm. Since weak contraction of pelvic floor muscles reduce sexual function, PFD has a great impact on sexual function[29]. The anatomical and physiological problem in pelvic floor in relation to POP and SUI interferes with sexual function because women lose sexual desire, unable to attain orgasm, and feel pain during intercourse. All these are, in turn, caused by the underlying problem of PFD and the women's negative self-image of unattractiveness in relation to changes to their bodies. In addition to this, women with PFD exhibit poor quality of life and low self-esteem both of which further exacerbate sexual dysfunction[9,11]. Parity is significantly associated with FSD. Large number of children can negatively affect the intimacy of couples, and lower marital sexual relationships[4,30]. Educated women have increased awareness of sexual needs and rights and are more likely to have positive sexual experience[5,30].

Sexual dysfunction was 12% higher among Khat (*Catha edulis*) consumed participants compared to non Khat (*Catha edulis*) consumer participants. Khat is a psychostimulant plant commonly chewed in certain countries of East Africa[31]. The relationships of Khat (*Catha edulis*) chewing and sexual function is not clear. Studies revealed that consuming Khat (*Catha edulis*) has a negative impact on male sexual function by inducing erection problem and impotence. Its relationship with female sexual function is not yet established[31,32]. In general, this study was conducted in an established Health and Demographic Surveillance System, which provided a robust platform to randomly select participants, thus it is possible to generalize this finding to women in rural Eastern Ethiopia. In addition, we used the FSFI questionnaire, which has been tested in different parts of the world; the questionnaire has good internal consistency.

Study Limitations

The findings relied on self-reported data, which are subject to recall and desirability bias. We would like to stress that, because revealing sexual function is associated with cultural taboos, the participant women in this study might have hesitated to adequately respond to the data collectors. Thus, they might have underreported their sexual experiences. Consequently, this might underestimate the prevalence of sexual dysfunction. To minimize the impact of these aspects, the participants were interviewed by female data collectors in a private setting.

Conclusion

About half of the women in the study community had sexual dysfunction. PFDs increase the prevalence of sexual dysfunction by 56%. This calls for an urgent need to initiate interventions against PFD to promote womens' reproductive health.

Ethics

Ethics Committee Approval: The study protocol was approved by Haramaya University Health and Medical Sciences College Institutional Health Research ethics review committee (approval number: IHRERC /001/2016).

Informed Consent: Consent form was filled out by all participants. In order to protect the confidentiality of the information, names and identification was not included in the written questionnaires.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.D., L.O., B.M., N.A., Concept: M.D., Y.B., A.W., L.O., B.M., N.A., Design: M.D., Y.B., A.W., L.O., B.M., N.A., Data Collection or Processing: M.D., L.O., B.M., N.A., Analysis or Interpretation: M.D., A.W., L.O., N.A., B.M., Y.B., Literature Search: M.D, Writing: M.D., Y.B., A.W., L.O., B.M., N.A.

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Analysis of two different luteal phase support regimes and evaluation of *in vitro* fertilization-intra cytoplasmic sperm injection outcomes

İki farklı luteal faz destek rejiminin analizi ve in vitro fertilizasyon-intrasitoplazmik sperm enjeksiyonu sonuçlarının değerlendirilmesi

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Abstract

Objective: To evaluate clinical pregnancy rates, miscarriage rates, ongoing pregnancy rates, and *in vitro* fertilization-intra cytoplasmic sperm injection outcomes of gonadotropin releasing hormone agonist (GnRHa) administration compared with human chorionic gonadotropin (hCG) application for luteal phase support.

Materials and Methods: A total of 456 patients were included in the study. The patients were divided into two groups according to luteal phase support type: in group 1 (n=158), single-dose triptorelin acetate 0.1 mg was given on the sixth day after the oocyte pick-up (OPU). In group 2 (n=298), hCG 1500 IU was given on day 4, 7 and 10 after the OPU.

Results: Both groups were homogeneous in relation with age and antral follicle count. The number of stimulation days and endometrial thickness on hCG day (mm) were found to be significantly higher in group 2 than in group 1 (p<0.001). The clinical pregnancy rate was slightly higher in the GnRHa group, but this difference was not statistically significant.

Conclusion: Although there was no statistically significant difference between the two groups, luteal phase support with single-dose GnRHa might be as efficient as three doses of hCG. Large prospective, randomized-controlled studies are required comparing GnRHa and hCG for luteal phase support.

Keywords: Luteal phase support, gonadotropin-releasing hormone agonist, infertility, in vitro fertilizationn-intra cytoplasmic sperm injection

Öz

Amaç: Bu çalışmanın amacı luteal faz desteği için human koriyonik gonadotropin (hCG) ile gonadotrophin-releasing hormone agonist (GnRHa) verilen hastaların klinik gebelik oranlar, abortus oranları, devam eden gebelik oranları ve *in vitro* fertilizasyon-intrasitoplazmik sperm enjeksiyonu sonuçlarını karşılaştırmaktır.

Gereç ve Yöntemler: Toplam 456 hasta çalışmaya dahil edildi. Hastalar luteal faz desteğine göre iki gruba ayrıldı. Grup 1'e (n=158), oosit toplamadan (OPU) 6 gün sonra triptorelin asetat 0,1 mg tek doz verildi. Grup 2'ye (n=298) OPU'dan sonraki 4, 7, ve 10. günlerde 1500 IU hCG verildi.

Bulgular: Yaş ve antral folikül sayısı açısından her iki grup homojendi. Stimülasyon gün sayısı ve hCG günündeki endometrial kalınlık (mm) grup 2'de grup 1'den anlamlı şekilde daha yüksekti (p<0,001). Klinik gebelik oranı GnRHa grubunda hafif şekilde daha yüksekti ancak, aradaki fark istatistiksel olarak anlamlı değildi.

Sonuçlar: Her iki grup arasında istatistiksel olarak anlamlı bir fark bulunmamasına rağmen, GnRHa ile tek doz luteal faz desteği hCG ile 3 doz destek verilmesi kadar etkili bulunmuştur. GnRHa ile hCG'nin luteal faz desteği olarak karşılaştırıldığı daha büyük prospektif randomize kontrollü çalışmalara ihtiyaç duyulmaktadır.

Anahtar Kelimeler: Luteal faz desteği, gonadotropin salgılatıcı hormon agonisti, infertilite, *in vitro* fertilizasyon-intrasitoplazmik sperm enjeksiyonu

PRECIS: There was no gap with GnRHa for luteal support.

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Introduction

In vitro fertilization (IVF) - intra cytoplasmic sperm injection (ICSI) has been used worldwide for more than two decades and embryo implantation is a major component of this procedure. Optimization of endometrial receptivity is essential for a successful implantation[1]. Supraphysiologic estradiol (E_2) levels due to controlled ovarian hyperstimulation (COH) lead to a decrease in luteinizing hormone (LH) levels. The corpus luteum may not be functional in the absence of LH. The occurrence and maintenance of pregnancy necessitates adequate secretion of progesterone from the corpus luteum[2,3]. Dysfunction of the corpus luteum results with low progesterone levels. Therefore, a progesterone supplement is administered during the luteal phase to achieve optimal endometrial receptivity[4]. There are many protocols of luteal support in assisted reproductive technology (ART) cycles. Luteal phase support with progesterone is a standard approach for ART cycles[5]. Progesterone can be used via oral, intramuscular, and transvaginal routes. However, there is still debate about the starting time and continuation. Transvaginal progesterone is commonly used for luteal phase support. Progesterone administration is initiated on the oocyte pick-up (OPU) day and continued for 12 days, until the serum beta human chorionic gonadotropin (hCG) measurement day. However, there are conflicting results regarding the dose, route of administration (oral, subcutaneous, transvaginal), duration (until the ultrasound demonstration of heartbeat in an intrauterine gestational sac, until 10 weeks of gestation, until 12 weeks of gestation), and formulations such as synthetic or micronized types of progesterone. Although some studies indicated that transvaginal progesterone use was efficient for luteal phase support, Vaisbuch et al.[6] reported that further studies were necessary for this subject. Pritts et al.[7] reported that the addition of E_2 to progesterone could be more effective on IVF-ICSI outcomes. A Cochrane review was reported by Daya et al.[8] regarding luteal phase support in ART cycles. The authors concluded that luteal phase support with hCG or progesterone after ART was associated with an increased clinical pregnancy rate [odds ratio (OR) 1.34, 95% confidence interval (CI): 1.01-1.79]. They found that luteal phase support with hCG had grater Ovarian hyperstimulation syndrome (OHSS) risk than progesterone (OR 3.06, 95% CI: 1.59-5.86). Luteal phase support with gonadotropin releasing hormone agonist (GnRHa) was first described by Tesarik et al[9]. They found that GnRHa might have a direct effect on the embryo. Other theories about GnRHa are its flare-up action and direct effect on endometrium[10]. Although there are many studies about the use of GnRHa as a supporter of luteal phase, the exact mechanism remains controversial. Besides, the results of these studies are conflicting[11,12]. Fusi et al.[13] administered GnRHa for luteal support in women at high risk for OHSS undergoing IVF. They concluded that luteal support with GnRHa could be used as the first choice in patients at high risk for OHSS. Engman et al.[14] found that a GnRHa trigger was effective in the prevention of OHSS during IVF treatment. A current Cochrane review was reported by van der Linden et al.[15] about luteal phase support in subfertile women undergoing assisted reproduction. They reported that the addition of GnRHa to progesterone was associated with an improvement in pregnancy outcomes. For this reason, we aimed to compare two different luteal phase support regimes, GnRHa and hCG, and to assess IVF-ICSI outcomes.

Materials and Methods

Study design

This study was designed as a prospective cohort trial. In total, 456 women aged between 25 and 38 years were included in the study. The data of the patients were collected from patients who presented to the IVF unit of Ankara Zekai Tahir Burak Women's Health Training and Research Hospital. The study protocol and ethical consent was approved by the local ethics' committee. The patients were divided into two groups according to luteal phase support type. Group 1 contained patients who received single-dose triptorelin acetate 0.1 mg. Group 1 included women who underwent IVF-ICSI one year prior to the beginning of the study. Accordingly, this line of the study was retrospective. Group 2 included patients who received hCG 1500 IU, which was given on day 4, 7, and 10 after the OPU. Group 2 joined the study six months after the onset of the study; therefore, this line of the study was prospective. Luteal phase support was given with hCG or GnRHa for 1 year and with GnRHa for six months, in addition to transvaginal progesterone. Subjects who had undergone frozen-thawed embryo transfer and those with male factor infertility were not included in the study. Normoresponder patients were included in the study. Exclusion criteria were having follicle-stimulating hormone (FSH) >15 IU/L, anti-mullerian hormone level <1.0 ng/mL, and an antral follicle count (AFC) <4 on the second day of menstruation. First fresh cycles of all patients were included in the study. Single embryo transfer was performed in all subjects according to legal requirements.

Gonadotropin stimulation for assisted reproductive technique, oocyte retrieval, and sample collection

All patients were treated with an antagonist protocol, and an hCG trigger was used for final maturation. Flexible daily GnRH antagonist protocol was preferred to induce pituitary down regulation (Cetrotide® 0.25 mcg, Merck-Serono, Switzerland). One hundred fifty-two hundreds twenty five IU daily rec-FSH (Gonal-F®, Merck-Serono, Switzerland) and/or human menopausal gonadotropin (Menogon®, Ferring, Germany) were started on day 3 of the cycle and continued for the first 3 days of stimulation, after which daily dosing was determined individually. The GnRH antagonist was started when the leading follicle reached a diameter of 12-14 mm.

Serial E_2 levels and two-dimensional follicle measurements using transvaginal ultrasound imaging (Logic 200 Pro®, General Electric, Korea) were performed until at least two dominant follicles reached dimensions of 18 mm or greater in diameter. Human chorionic gonadotropin (Pregnyl® 10.000 U I.M., Organon, Netherland) was administered, followed by transvaginal oocyte retrieval 36 h later. ICSI was performed in all patients. Single embryo transfer was used because of legacy. Embryos were classified according to the number of blastomeres, percentage of fragmentation, and blastomere appearences on the first, third, and fifth days. All transfers were made using Rocket ThinWall Transfer Sets (Rocket Medical, Hingham, MA, USA). The patients were allocated into two groups according to luteal phase support type: in group 1 (n=158), single-dose GnRHa triptorelin acetate (Decapeptyl® Ferring, Germany) 0.1 mg was given on the sixth day after the OPU. In group 2 (n=298), hCG 1500 IU was given on days 4, 7, and 10 after the OPU. All women were administered vaginal progesterone (Crinone 8% vaginal gel®, Merck-Serono, Switzerland) 90 mg daily starting on the day of oocyte retrieval and lasting for 12 days (until the day of serum β hCG measurement). If pregnancy occurred, progesterone was given until 12 weeks of gestation. Clinical pregnancy was diagnosed through the ultrasound demonstration of heartbeat in an intrauterine gestational sac. Miscarriage rates and ongoing pregnancy rates were calculated.

Statistical Analysis

Statistical analysis was performed using the SPSS Ver. 15.00 (SPSS Inc., Chicago) statistics software package. Data normality was assessed using the Kolmogorov-Smirnov test. Statistical comparisons between groups were performed using the Mann-Whitney U (for unrelated samples) and Wilcoxon (for related samples) tests. The chi-square test was used for categorical variables and an independent Sample t-test was used for continuous variables that were normally distributed. P<0.05 was considered significant.

Results

In total, 456 women were included into the study. Single-dose triptorelin acetate was administered to 158 women. Three doses hCG were given to 298 women. The characteristics of the participants are shown in Table 1. Both groups were homogeneous in relation to patients' age, duration of infertility, basal FSH levels, basal E_2 levels, and AFC. There were no statistical differences in terms of these parameters. There were no differences between the groups regarding total gonadotropin dose, oocyte number, and metaphase 2 oocyte number (Table 2). Although the clinical pregnancy rate was slightly higher in the GnRHa group, the difference was not statistically significant (p=0.49). Miscarriage rates and live birth rates were not statistically significant between the two groups (p=0.12 and p=0.88, respectively). No systemic adverse effects were observed and no severe OHSS occurred.

Table 1. Characteristics of the patients

	GnRHa (n=158)	hCG (n=298)	p
Age (years)	29.5±4.5	28.4±3.7	0.08
Duration of infertility (year)	5.0±0.4	4.9±0.5	0.29
Basal FSH level (IU/L)	6.8±2.5	6.3±1.9	0.38
Basal E_2 level (pg/mL)	40.1±19.8	37.8±17.1	0.76
Antral follicle count	10.3±4.3	9.8±2.9	0.94

hCG: Human chorionic gonadotropin, GnRHa: Gonadotropin releasing hormone agonist, FSH: Follicle-stimulating hormone, E_2: Estradiol
p<0.05, means statistically significant

Table 2. Comparison of *in vitro* fertilization-intracytoplasmic sperm injection outcome according to the luteal phase support

	GnRHa (n=158)	hCG (n=298)	p
Total gonadotropine dose (IU/L)	1983.7±877.9	2016.5±1212.3	0.36
Peak E_2 (pg/mL)	2128.6±1149.2	2372.3±1222.4	0.06
Oocyte number, n	9.9±5.3	9.5±5.0	0.45
Metaphase 2 oocytes, n	4.9±3.5	4.5±3.2	0.45
Number of transferred embryos	1.3±0.6	1.5±0.8	0.31
Clinical pregnancy rate, n (%)	58 (36.7%)	96 (32.2%)	0.49
Miscarriage rate per pregn., n (%)	11 (18.9%)	14 (14.5)	0.12
Live birth rate, n (%)	41 (25.9)	73 (24.4)	0.88

GnRHa: Gonadotropin releasing hormone agonist, hCG: Human chorionic gonadotropin, E_2: Estradiol, Pregn: Pregnancy, p<0.05, means statistically significant

Discussion

In this cross-sectional study, we aimed to compare the efficacy of two different luteal phase support regimes (triptorelin acetate and hCG) and to evaluate IVF-ICSI outcomes. The results of our study demonstrated that administration of triptorelin acetate (GnRHa) might be as efficient as hCG as an agent for luteal phase support. Our results were consistent with previous studies[8,12]. COH with GnRH agonists or antagonists has been used to prevent premature luteinization in ART cycles. However, these agents may inhibit the function of the corpus luteum by decreasing LH levels[16]. Therefore, luteal phase support in ART cycles has been taken into consideration to avoid this inhibition. Also, these drugs could have direct effects on the endometrium and embryo. According to the world data, those applied drugs were different from others for luteal support[6].

Tesarik et al.[9] first reported that supplementation of single-dose 0.1 mg triptorelin could enhance IVF-ICSI outcomes.

The effect of GnRHa given during luteal phase on clinical pregnancy rates is still unclear. On the other hand, GnRHa receptors have been found on the embryo and endometrium. It is speculated that single-dose GnRHa administered during the luteal phase could enhance implantation because it decreases rates of abortion and OHSS, and increases multiple pregnancy rates[17,18]. We had no cases of multiple pregnancy because single embryo transfer was performed in all subjects. Pirard et al.[19] suggested that, the addition of a GnRHa (buserelin) during the luteal phase of IVF cycles might be effective for luteal phase support. On the contrary, Ata et al.[20] found that single-dose 0.1 mg triptorelin administration 6 days after ICSI did not increase ongoing pregnancy rates. In our study, miscarriage rates and live birth rates were not statistically significantly different between the two groups (p=0.12 and p=0.88, respectively). The primary endpoint of the present study was to compare the live birth rate. These results were our preliminary findings. The limitations of our study were the restricted number of patients and its retrospective nature. Van der Linden et al.[21] reported that progesterone enhanced the implantation rate, pregnancy rate, and live birth rate. Even though the route of administration did not affect the results, vaginal and intramuscular progesterone were found to be more efficient than the other routes[21]. The above-mentioned studies suggested that vaginal progesterone was sufficient for luteal phase support. However, the ideal method remains unclear and the preferences for use are different.

A recent meta-analysis by Kyrou et al.[22] reported on the influence of luteal single-dose GnRHa on IVF-ICSI outcomes. They performed a computerized literature search up until December 2010. From the 38 studies yielded, 6 randomized controlled trials (RCT) were analyzed. The authors concluded that the addition of GnRHa during the luteal phase increased live birth rates. Another recent meta-analysis by Martins et al.[23] documented the effect of GnRHa during the luteal phase for women undergoing ARTs. They found that the use of GnRHa as a luteal phase supporter was still controversial because there was no evidence with respect to adverse perinatal outcomes and congenital malformations. Our results indicate that there was no difference between the GnRHa group and the hCG group in terms of pregnancy rates. The purpose of our study was to compare hCG versus GnRHa protocols as luteal phase support regimes and to evaluate IVF-ICSI outcomes.

Conclusion

In conclusion, there were no differences in live birth rates between luteal GnRHa and hCG administration in addition to transvaginal progesterone. However, large RCTs are required to determine the effect of luteal phase support with GnRHa on IVF-ICSI outcomes.

Ethics

Ethics Committee Approval: The study protocol and ethical consent was approved by the local ethics' committee (approval number: 45/date:24.03.2014).
Informed Consent: Retrospective study.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.K.Y., A.S., Concept: N.K.Y., M.K., S.E., Design: N.K.Y., M.K., Data Collection or Processing: N.H., B.C., Analysis or Interpretation: S.E., M.K., Writing: M.K., N.K.Y.
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Evaluation of platelet-rich plasma injection activity in the treatment of abnormal uterine bleeding

Anormal uterin kanamanın tedavisinde plateletten zengin plazma enjeksiyonunun etkinliğinin değerlendirilmesi

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Abstract

Objective: To evaluate the effectiveness of intracavitary platelet-rich plasma (PRP) therapy in patients diagnosed as having abnormal uterine bleeding (AUB).

Materials and Methods: A total of 149 patients with AUB were included in the study. Seventy-four of these patients were included in the study group and 75 were included in the control group. All patients were evaluated using transvaginal ultrasonography. Endometrial curettage was performed to exclude underlying organic pathologies. The study group underwent intracavitary PRP therapy. Both patient groups were called for follow-up at the end of the third month. Their endometrial thickness and amount of bleeding (pictogram and pads/day) were evaluated using transvaginal ultrasonography.

Results: There was no statistically significant difference between the study and control groups in terms of the decrease in the amount of bleeding. In addition, there was no statistically significant difference between the two groups in terms of the increase in endometrial thickness.

Conclusion: In this study, it was observed that intracavitary PRP therapy did not make a significant difference in the decrease in the amount of bleeding and in the increase in endometrial thickness between the study and control groups.

Keywords: Abnormal uterine bleeding, growth factors, platelet-rich plasma

Öz

Amaç: Bu çalışmada amaç, abormal uterin kanama (AUK) tanısı alan olan olgularda intrakaviter plateletten zengin plazma (PRP) tedavisinin etkinliğinin değerlendirilmesidir.

Gereç ve Yöntemler: Araştırmaya kliniğimizin jinekoloji polikliniğine aşırı vajinal kanama şikayeti ile başvuran ve AUK tanısı alan 149 hasta dahil edilmiştir. Bu hastaların 74'ü çalışma grubunu, 75'i kontrol grubunu oluşturmuştur. Tüm hastalara transvajinal ultrasonografi ile değerlendirme yapılıp, altta yatan organik patolojileri ekarte etmek için endometriyal küretaj yapılmıştır. Çalışma grubuna intrakaviter PRP tedavisi uygulanmıştır. Her iki hasta grubu da 3. ay sonunda değerlendirilmek üzere kontrole çağrılmış ve transvajinal ultrasonografi ile endometrial kalınlıkları ve kanama miktarları (pictogram ve ped/gün) değerlendirilmiştir.

Bulgular: AUK nedeniyle intrakaviter PRP tedavisi uygulanan grupta kanama miktarındaki azalmanın kontrol grubuna göre istatistiksel olarak farkı olmadığı görüldü. Ek olarak her iki hasta grubunda endometriyal kalınlık artışı arasında da istatistiksel olarak fark izlenmedi.

Sonuç: Yapılan çalışmada intrakaviter PRP tedavisinin, çalışma ve kontrol grupları arasında hem kanama miktarı, hem de endometriyal kalınlık artışı üzerinde her iki grupta da anlamlı bir fark yaratmadığı gözlendi.

Anahtar Kelimeler: Anormal uterin kanama, büyüme faktörleri, platelet rich plazma

PRECIS: This study was conducted to investigate the effect of platelet rich plasma on abnormal uterine bleeding and endometrial thickness.

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Introduction

Abnormal uterine bleeding (AUB) is the bleeding of organic or non-organic causes that indicate irregularity in the amount, duration, and frequency of menstrual bleeds[1,2]. AUB constitutes approximately one-third of the reasons for referral to hospital in gynecology practice. The acronym polyp; adenomyosis; leiomyoma; malignancy and hyperplasia; coagulopathy; ovulatory dysfunction; endometrial; iatrogenic; and not yet classified, which classifies uterine bleeding abnormalities by bleeding pattern and etiology in reproductive-age women, was published by the International Federation of Gynecology and Obstetrics in 2011. The term menorrhagia was later replaced by heavy menstrual bleeding, and the term metrorrhagia was replaced by intermenstrual bleeding[3-5]. It can be treated medically or surgically. The idea of using platelet-rich plasma (PRP) for therapeutic purposes has emerged because platelets contain high amounts of growth factors and are the main source of growth factor complexes that play a key role in the wound healing process. PRP is defined as plasma fraction of autologous blood having a platelet concentration above baseline[6,7]. PRP is a cellular component of plasma, which is obtained by centrifuging whole blood, and contains a higher platelet concentration than whole blood. The cellular component of plasma is normally composed of 93% red blood cells, 6% platelets, and 1% leukocytes. PRP contains about 3-5 times the number of platelets found in normal blood circulation. PRP is basically a reversal of ratio between red blood cells and platelets; and is made up of 93% platelets, 6% red blood cells, and 1% leukocytes[8]. Enzyme-linked immunosorbent assay and immunoprecipitation studies have shown that there is a 7-fold increase in transforming growth factor-β, a 30-fold increase in platelet-derived growth factor, and a 10-fold increase in epidermal growth factor[9]. *In vitro* and animal studies have demonstrated that PRP positively affects gene expression, matrix synthesis, and vascularization in tendon cells[10]. Today, it is used mostly in surgical procedures such as orthopaedic interventions, dental and oral surgery, traumatic surgical procedures, maxillofacial surgery, spinal surgery, heart bypass surgery, angiogenic interventions, sliding flap operations, and surgical repair of macular lesions and corneal epithelial defects. Although it is not used very frequently in the field of gynaecology, it is used particularly in infertility treatment and in patients with recurrent miscarriages, as well as in postoperative wound treatment. It has been observed that PRP therapy for infertility issues increases endometrial growth and improves pregnancy outcomes in patients with a thin endometrial lining[11]. In summary, it has been concluded that PRP has a regulatory role on endometrial inflammation and thereby provides a rapid proliferation process and maintains endometrial tissue integrity in the long term[12]. However, there are still few studies in the field of gynecology in the literature. In this study, we aimed to investigate the effect of intracavitary PRP injections on the amount of bleeding and endometrial thickness at the end of 3 months in patients with AUB aged between 20 and 40 years.

Materials and Methods

Our study was performed prospectively after approval was obtained from the Local Ethics Committee of University of Health Sciences Kanuni Sultan Süleyman Training and Research Hospital. A total of 149 patients, who were admitted to the obstetrics and gynecology outpatient clinic due to AUB between March 1st, 2017, and June 1st, 2017, were included in the study. Reproductive-aged patients aged between 20 and 40 years and who had AUB resistant to drugs were included in the study. Patients who did not fit the age range, who had hormonal disturbances and additional systemic diseases, and who had endometrial pathology (polyp, myoma) were excluded from the study. One hundred sixty patients were randomly divided into two equal groups of 80 each: the study group and the control group. Six of the 80 patients in the study group and 5 of the 80 patients in the control group were excluded from the study because they did not come to follow-up in the third month. During the evaluation phase, the uterine cavity was first evaluated using transvaginal ultrasonography. The amount of bleeding (pictogram and pads/day) was recorded. The double-wall endometrial thickness was measured in the sagittal plane. Then, hormone markers [follicle-stimulating hormone (FSH), leutinizing hormone (LH), estradiol (E_2), and thyroid-stimulating hormone (TSH)] were analyzed. After clinical evaluation, 74 patients who were randomized by the computer program underwent a complete curettage. A total of 30 cc venous blood was collected into 3 EDTA tubes from these patients using a butterfly needle. The blood samples were centrifuged at 3200 rpm for approximately 15 minutes. The PRP fraction (buffy coat), which was separated from the whole blood by centrifugation and remained on the tube, was pulled and collected using a syringe needle. Approximately 3-4 cc PRP was obtained from 30 cc venous blood. The prepared PRP material was introducced to the uterine cavity using a cannula within 10 minutes from collection. The patients were kept in bed for about 10 minutes. A total of 75 patients in the control group underwent a complete curettage after clinical evaluation and no additional intervention was performed. The patients were discharged after their general condition was stabilized and called to return for follow-up at the end of the third month. Both groups were asked to keep a diary of bleeding for 3 months. They were called for follow-up in the follicular phase of the menstrual cycle 3 months later. Bleeding issues observed in the patients after 3 months were questioned and recorded. The double-wall endometrial thickness was measured using transvaginal ultrasonography.

Statistical Analysis

All results are expressed as mean +/- standard deviation. The relationships between the variables were assessed using Pearson's correlation test. The one-sided Kolmogorov-Smirnov test was used to assess the distribution of the data. Student's t-test was used to compare normally distributed data between the two groups. The chi-square test was used to examine categorical data. Two-way analysis of variance was used to assess the effects on the independent variables in the study and control groups. A p value of <0.05 was considered statistically significant. All statistical analyses were performed using the SPSS statistical software, version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

The mean age of the study group was 26.87±5.40 years, and the mean age of the control group was 28.19±4.93 years (p=0.420). The demographic characteristics of the two groups are shown in Table 1. As seen in Table 1, when the demographic data of the study and control groups were compared, the two groups were similar in terms of age, body mass index, gravidity, parity, abortion, FSH value, and amount of bleeding at first admission (pads/day). Endometrial thickness was evaluated in the follicular phase of the menstrual cycle using transvaginal ultrasonography at the end of the third month in the control and study groups. The mean endometrial thickness was 7.8 mm in the study group and 9 mm in the control group. No statistically significant difference was found between the two groups (Table 2). The amount of bleeding at the end of the third month was evaluated based on the number of pads/day in the control and study groups. The mean amount of bleeding at first admission was 7 pads/day in the study group and 6 pads/day in the control group (Table 1). As seen in Table 3, it was found that the two groups were similar in terms of the amount of bleeding at the end of the third month. There was no statistically significant difference between the two groups in terms of the amount of bleeding at the end of the third month.

Table 1. Demographic characteristics of the study and control groups

	Study group (n=74)	Control group (n=75)	p
Age	26.87±5.40	28.19±4.93	0.420
BMI	25.88±3.91	26.07±3.71	0.732
Gravidity	2.58±1.31	2.65±1.56	0.162
Parity	2.11±1.08	2.1±1.2	0.24
Abortion	0.5±0.13	0.85±0.47	0.13
FSH value	8.64±2.78	7.74±3.31	0.135
Amount of bleeding (pads/day)	7.72±0.11	6.92±0.17	0.162

BMI: Body mass index, FSH: Follicle-stimulating hormone

Table 2. Endometrial thickness values at the end of the third month in the study and control groups

	Study group (n=74)	Control group (n=75)	p
Endometrial thickness (mm)	7.8±4.4	9.0±4.7	0.138

Table 3. The amount of bleeding at the end of the third month in the study and control groups

	Study group	Control group	p
Amount of bleeding (pads/day)	5.2±2.9	4.6±2.9	0.180

Discussion

AUB accounts for 10-15% of gynecologic problems. It is most commonly seen at the beginning (after menarche) and the end (perimenopausal period) of the reproductive life cycle (70%). Fifty percent is seen after the ages of 40 years and 20% is seen during adolescence. The remaining 30% is seen in the reproductive period. One out of every 20 women aged between 30-49 years is admitted to hospital due to AUB. There is no pathologic reason for approximately half of these. PRP is used especially for postoperative wound healing in gynecology. Moreover, it is injected into the uterine cavity in infertile patients or in patients with recurrent miscarriages and thus it benefits from growth factors in its content[11,13,14]. The age range of our study was selected as 20-40 years. The effect of PRP on AUB was examined particularly in reproductive-aged patients. Patients who had previously received various medical treatments for AUB but continued to report problems despite these medical treatments were included in the study. FSH, LH, E_2, and TSH values were analyzed in the patients. Patients with polycystic ovary syndrome, low ovarian reserve, and thyroid dysfunction were not included in the study. Furthermore, patients with additional systemic diseases and who had organic uterine pathologies were excluded from the study. The two groups were similar in terms of demographic data and the amount of bleeding at first admission. The main reason why the patients in the study group underwent a complete curettage prior to PRP therapy was to increase the endometrial blood flow except for pathologic diagnosis and to allow the diffusion of PRP into the endometrium. Although there are not many publications related to PRP in the field of gynecology in the literature, it has been tested in assisted reproductive technique (ART) treatments. In our

study, intracavitary PRP injection was applied as used in ART treatments. Patients were evaluated in terms of decreases in the amount of bleeding and increases in endometrial thickness. Significantly different results were obtained in PRP studies using ART. In the pilot study of Zadeh-Modarres et al.,[15] 10 patients with history of inadequate endometrial growth in frozen-thawed embryo transfer cycles were evaluated. Intrauterine infusion of PRP was performed in these patients. They reported that all patients had increased endometrial thickness and some patients had chemical and clinical pregnancies. On the contrary, our study found that although endometrial thickness at the end of the third month was thinner in the study group than in the control group, there was no statistically significant difference between the two groups. In the study of Tandulwadkar et al.,[14] PRP was administered to the uterine cavity in 68 patients who had recurrent cycle cancellation due to endometrial insufficiency and received ART treatment. PRP was used to achieve the optimal endometrial thickness in these patients. It was concluded that endometrial thickness increased from 5 mm to 7.2 mm in patients who underwent PRP therapy in the cycle before the procedure. In the same study, patients with a thin endometrium who were treated with PRP were evaluated before and after treatment using Doppler ultrasonography, which revealed increased tissue vascularization. Based on these findings, they reported that PRP enhanced angiogenesis and had a proliferative effect on the endometrium[14]. Chang et al.[11] showed a similar effect in their study. PRP injection was administered to patients who were scheduled for *in vitro* fertilization (IVF) treatment on the 10th day of hormone replacement therapy prior to the embryo transfer. The cut-off value of endometrial thickness on the 7th day (embryo transfer day) was considered as 7 mm, and endometrial thickness was measured using transvaginal ultrasonography. Women with endometrial thickness >7 mm underwent IVF-embryo transfer. A live pregnancy was achieved in all women who underwent PRP therapy. In contrast, our study found that the increase in endometrial thickness was not significant. In the *in vivo* study of Marini et al.[12] performed in the bovine endometrium, it was concluded that PRP had a regulatory role on endometrial inflammation and thereby provided a rapid proliferation process and maintained endometrial tissue integrity in the long-term. In the study of Challen et al.,[16] it was mentioned that stem cell studies on the endometrium clearly revealed the effect of stem cells on the regenerative process and that growth factors supported this process. The regenerative process progressed rapidly and the tissue integrity quickly returned to normal because the PRP we used was similarly rich in growth factors. However, this process ultimately did not reflect on the decrease in the amount of bleeding and the increase in endometrial thickness. In the study of Hang-Yong Jang et al.[17], endometrial injury was first achieved in 60 female rats using ethanol. PRP therapy was applied after 72 hours, and tissue sampling was performed in the mid-luteal phase. Subsequently, there was an increased rate of proliferation of endometrial tissue stained with hematoxylin and eosin and Masson's trichrome staining. Pathologic data have proven that PRP therapy enhances regeneration. In our study, the ethanol-induced endometrial damage was mechanically achieved through complete curettage, and then PRP injection was performed. However, the proliferation level did not reach statistical significance in the study group compared with the control group. On the contrary, endometrial thickness was found to be lower in the study group than in the control group.

Our study has some limitations. The patients received only a single dose of PRP. Measurements were only made in 3 months after administration. Therefore, the effect of repeated doses of PRP and its longer-term effect could not be assessed. Longer-term studies are needed to investigate whether PRP provides tissue integrity and regeneration in the long term.

Conclusion

As a result of this study, it was determined that there was no statistically significant difference in the amount of bleeding between the group that had AUB and underwent PRP therapy and the control group. Unlike previous studies, it was seen that the increase in endometrial thickness was less in the PRP-treated group than in the control group. There are many unanswered questions about the composition of PRP, the characteristics of individual blood products, different production protocols, different application methods, and effect mechanisms applied at the cellular level by PRP and its individual components. Although there are few publications in the literature about the effects of PRP on the endometrium, this relationship can be explained more clearly by future studies.

Ethics

Ethics Committee Approval: The study was approved by the Local Ethics Committee of University of Health Sciences Kanuni Sultan Süleyman Training and Research Hospital (approval number: KAEK/2016/12.9)

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

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.T., Concept: G.T., P.Y.B., Design: G.T., P.Y.B., B.Y.Ö., Data Collection or Processing: G.T., Analysis or Interpretation: P.Y.B., A.A.A., Literature Search: G.T., P.Y.B., Writing: G.T., P.Y.B.

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Risk factors for eclampsia in pregnant women with preeclampsia and positive neurosensory signs

Preeklampsi ve pozitif nörosensör belirtileri olan gebelerde eklampsi için risk faktörleri

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Abstract

Objective: In Morocco, eclampsia remains the second major cause of maternal mortality. Conventionally, patients with preeclampsia and neurosensory signs (NSS) (e.g., headaches and hyperreflexia) are considered at high risk of worsening and progressing to eclampsia. However, this specific population is heterogeneous in terms of eclampsia occurrence. We aimed to identify the risk factors for the development of eclampsia in women with preeclampsia presenting with NSS at admission.

Materials and Methods: We performed a single-center, retrospective case-control study of patients with preeclampsia with positive NSS from January 1st, 2012 through December 31st, 2015, to investigate predictive factors for eclamptic seizures. The case patients were pregnant women with severe preeclampsia who had NSS before developing eclampsia. Control subjects were those with positive NSS without the development of seizures during their hospital stay. One hundred-thirty eight patients with eclampsia and 272 control patients were enrolled.

Results: Univariate analysis revealed that eclampsia was more likely to develop in patients with the following risk factors: maternal age ≤25 years ($\chi2$=9.58, p=0.002), primiparity ($\chi2$=6.38, p=0.011), inadequate prenatal care ($\chi2$=11.62, p=0.001), systolic hypertension ≥160 mmHg ($\chi2$=15.31, p<0.001), diastolic hypertension ≥110 mmHg ($\chi2$=5.7, p=0.017), generalized acute edema ($\chi2$=14.66, p<0.001), hematocrit <35% ($\chi2$=11.16, p=0.001), serum creatinine >100 µmol/L ($\chi2$=13.46, p<0.001), asparate aminotransferase (AST) >70 IU/L ($\chi2$=10.15, p=0.001), and thrombocytopenia ($\chi2$=22.73, p<0.001). Additionally, independent predictive factors for eclampsia in multivariate analysis included inadequate prenatal care [odds ratio (OR), 8.96 [95% confidence interval (CI): 3.9-20.5], p<0.001), systolic blood pressure ≥160 mmHg (OR, 3.130 [95% CI: 1.342-7.305], p=0.008), thrombocytopenia with a platelet count <50.000 (OR, 13.106 [95% CI: 1.344-127.823], p=0.027), AST ≥70 IU (OR, 3.575 [95% CI: 1.313-9.736], p=0.007), and elevated liver enzymes level, and low platelet count (ELLP) syndrome, which is an incomplete variant of HELLP syndrome (H for hemolysis) (OR, 5.83 [95% CI: 2.43-13.9], p<0.001).

Conclusion: This work highlights two major risk factors in this patient population, inadequate prenatal care and ELLP syndrome, which can help in the early identification of patients at highest risk of developing eclampsia and guide preventive measures.

Keywords: Eclampsia, preeclampsia, development, neurosensory signs, risk factors

Öz

Amaç: Eklampsi, Fas'ta maternal mortalitenin ikinci ana nedeni olmaya devam etmektedir. Konvansiyonel olarak, preeklampsi ve pozitif nörosensör belirtileri (NSB) olan hastalar (örneğin; baş ağrısı ve hiperrefleksi), kötüleşme ve eklampsiye ilerleme riski yüksek olarak kabul edilmektedir. Bununla birlikte, bu spesifik populasyon eklampsi oluşumu açısından heterojendir. Bu çalışmada, NSB ile başvuran preeklampsili kadınlarda, eklampsinin gelişimindeki risk faktörlerinin belirlenmesi amaçlanmıştır.

Gereç ve Yöntemler: Eklamptik nöbetler yönünden prediktif faktörleri araştırmak amacıyla, 1 Ocak 2012-31 Aralık 2015 tarihleri arasında preeklampsi pozitif NSB'li hastaların tek merkezli, retrospektif bir olgu-kontrol çalışması gerçekleştirilmiştir. Olgudaki hastalar, eklampsi gelişiminden önce NSB'si olan şiddetli preeklampsili gebe kadınlar idi. Kontrol grubu, hastanede kaldıkları süre boyunca nöbet gelişimi olmadan pozitif NSB'ye sahip hastalardı. Eklampsili 138 hasta ve kontrol olarak alınan 272 birey çalışmaya dâhil edildi.

Bulgular: Tek değişkenli analiz, aşağıdaki risk faktörleri olan hastalarda eklampsinin gelişme olasılığının daha yüksek olduğunu ortaya çıkarmıştır; maternal yaş ≤25 yıl ($\chi2$=9,58, p=0,002), primipar ($\chi2$=6,38, p=0,011), yetersiz prenatal bakım ($\chi2$=11,62, p=0,001), sistolik hipertansiyon ≥160 mmHg ($\chi2$=15,31, p<0,001), diyastolik hipertansiyon ≥110 mmHg ($\chi2$=5,7, p=0,017), yaygın akut ödem ($\chi2$=14,66, p<0,001), hematokrit <%35 ($\chi2$=11,16, p=0,001), serum kreatinin >100 µmol/L ($\chi2$=13,46, p<0,001), asparate aminotransferase (AST) >70 IU/L ($\chi2$=10,15, p=0,001) ve trombositopeni ($\chi2$=22,73, p<0,001). Ek olarak, çok değişkenli analizde eklampsi için bağımsız öngördürücü faktörler yetersiz prenatal bakım (odds oranı (OR), 8,96

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[%95 güven aralığı (GA): 3,9-20,5], p<0,001), sistolik kan basıncı ≥160 mmHg (OR, 3,130 [%95 GA: 1,342-7,305], p=0,008), trombosit sayısı <50,000 olan trombositopeni (OR, 13,106 [%95 GA: 1,344-127,823], p=0,027), AST ≥70 IU (OR, 3,575 [%95 GA: 1,313-9,736], p=0,007) ve hemoliz yüksek karaciğer enzimleri ve düşük trombosit (HELLP) sendromunun eksik bir varyantı olan ELLP sendromunu (OR, 5,83 [%95 GA: 2,43-13,9], p<0,001) kapsamaktadır.

Sonuç: Bu çalışma, bu hasta popülasyonunda iki önemli risk faktörünün, yetersiz prenatal bakımın ve ELLP sendromunun, eklampsi gelişme riski en yüksek olan hastaları erken teşhis etmede ve önleyici tedbirlere yönlendirmede yardımcı olabileceğini vurgulamaktadır.

Anahtar Kelimeler: Eklampsi, preaklampsi, gelişim, nörosensör belirtiler, risk faktörleri

PRECIS: We have attempted, by carrying out a monocentric case-control study, to identify the predicting factors of eclampsia occurrence in a specific population: Preeclamptic women with positive neurosensory symptoms.

Introduction

Every day, at least 800 women die due to complications of pregnancy and delivery, equaling a death every two minutes and 292.000 deaths per year[1]. These complications are particularly overrepresented in developing countries[2]. Of these deaths, 12% are related to conditions of hypertension, among which eclampsia is one of the most urgent. Eclampsia is defined by the American College of Obstetricians and Gynecologists as new-onset of grand mal seizures in a woman diagnosed with preeclampsia, and is the second leading cause of maternal mortality in Morocco, after post-partum hemorrhage[3-5]. The efforts to predict which patients may suffer from preeclampsia and eclampsia have not yet resulted in a meaningful method of prevention, but the identification of certain predictive factors for the development of seizures in patients with preeclampsia can help caregivers optimize their plans and intervention strategies to prevent this serious, deadly pathology. The aim of the study was to identify predictive factors for the development of eclampsia in patients diagnosed with severe preeclampsia with positive neurosensory signs (NSS).

Materials and Methods

Study design

This was a retrospective case-control study performed in the Obstetrical Intensive Care Unit (OICU) at the Center for Mothers and Children in the Mohammed VI Hospital Center in Marrakech, Morocco. The inclusion period was from January 1st, 2012, through December 31st, 2015.

Patient population

The case group was defined as all patients who experienced preeclampsia with NSS at their admission in the OICU and who developed eclampsia during the inclusion period, and the control group was composed of all patients hospitalized in the same unit for severe preeclampsia with positive NSS. Positive NSS included one or more of the following: 1) persistent headaches resistant to treatment; 2) hyperreflexia, or; 3) visual troubles, including blurry vision, scotoma, floaters, photopsia, or temporal-cortical blindness. All patients included in the study underwent blood tests and, in addition to NSS, exhibited one or more of the following severe features of preeclampsia at admission: 1) Severe hypertension (systolic ≥160 mmHg and/or diastolic ≥110 mmHg); 2) Oliguria (<500 mL/24 hours); 3) serum creatinine concentration >100 µmol/L; 4) thrombocytopenia (platelet count <100.000/mm^3); 5) impaired liver function as attested by abnormally elevated blood levels of liver enzymes (to twice normal value), or; 6) acute pulmonary edema. Regarding the initial management targeting the stabilization of hospitalized patients, all women received the same local protocol (which is fully concordant with international recommendations), so a magnesium sulfate regimen was given. Nicardipine, a calcium channel blocker, was the first-line antihypertensive medication used and was carefully titrated to gradually lower the mean arterial blood pressure (BP) and mitigate abrupt variations of maternal BP. Moreover, both the preeclamptic parturient and the fetus benefited from close monitoring and surveillance and their statuses were frequently reassessed. Expedited and prompt delivery was considered, regardless of gestational age, in case of any worsening in maternal and/or fetal conditions. For stabilized women with viable fetuses aged less than 34 weeks of gestation, an antenatal schema of corticosteroids (12 mg per day of betamethasone) was administered within 2 days in order to induce fetal lung maturation.

Exclusion criteria

Patients were excluded if they developed seizures without associated gestational hypertension or had chronic epilepsy, meningitis, toxic or metabolic encephalitis, chronic hypertension, cerebral hemorrhage, or brain tumor.

Data collection

Data were collected from the archives of patient files in the OICU. Maternal variables gathered included age, past medical history, place of residence, gestational age when admitted to the unit, parity, the time between seizure and delivery, and the evolution of disease while the patient was in the unit. Physical exam variables collected included clinical symptoms at admission, Glasgow Coma score, BP, presence of edema, proteinuria, diuresis, hemoglobin, hematocrit, platelet counts, coagulation panel, liver function, bilirubin, and creatinine.

Statistical Analysis

Statistical analysis was performed using the SPSS, Version 20 (International Business Machines Corporation) software package. Data related to descriptive analysis were expressed as means, and bivariate analysis was achieved using the chi-square test (eclampsia occurrence was the dependent variable). Variables associated at the p<0.05 level in univariate analysis were entered into a multivariate logistic regression analysis. A final p value <0.05 was considered significant.

Results

Patient characteristics

From January 2012 through December 2015, 42.513 patients gave birth in our facility and 429 patients were found to fulfil the study criteria. The number of excluded cases was 19: ten patients due to diabetes, six due to a history of chronic hypertension, and three due to chronic renal insufficiency. The final analysis included 410 patients who met the inclusion criteria, with 138 patients in the study group (eclampsia group), and 272 patients in the control group.

Patient characteristics are detailed in Table 1. Notably, 42.8% of the eclampsia group was under the age of 25 versus only 27.6% of the control group, and the frequency of acute renal insufficiency in the eclampsia group was double that of the control group. Magnesium was used as an anticonvulsant in all cases. Of the 52 patients who had postpartum seizures, 47 (90.4%) were referred for postpartum eclampsia, 29 (61.7%) of whom gave birth at home. These data were unavailable in 16 patients (11.6%). The majority of observed deaths in the two groups results from cerebrovascular accidents (especially hemorrhage, sometimes with atypical locations such as the brainstem), disseminated intravascular coagulopathy, uncontrolled hemorrhagic shock (rupture of liver subscaplular hematoma or placental abruption), and finally multi-organ failure.

Outcomes

The analysis results are shown in Table 2. After completion of the univariate analysis, 13 independent risk factors for the development of eclampsia were identified as follows: patients aged 25 years old or younger (p=0.002), primiparous women (p=0.011), patients with inadequate prenatal care (p=0.001), patients with systolic BP ≥160 mmHg (p<0.001), diastolic BP ≥110 mmHg (p=0.017), patients with generalized edema (p<0.001), hemoglobin >12 g/dL (p=0.021), hematocrit <35% (p=0.001), thrombocytopenia with platelets <50.000/mm^3 (p<0.001) or 50.000-99.000/mm^3 (p<0.001), elevated liver enzymes with asparate aminotransferase (AST) >70 IU/L (p=0.001), creatinine >100 µmol/L (p<0.001), elevated liver enzymes level, and low platelet level (ELLP) (p<0.001), and cesarean birth (p=0.004). In the multivariate analysis, inadequate prenatal care (p<0.001), SBP >160 mmHg (p=0.008), thrombocytopenia with platelets ranging between 50.000 and 99.000/mm^3 (p<0.001) and <50.000/mm^3 (p=0.027), AST >70 IU/L (p=0.007), and ELLP syndrome (p<0.001) were independent variables that highly predisposed women with preeclampsia with positive NSS to eclampsia occurrence.

Discussion

Eclampsia is a serious disease, especially in developing countries where it is a major health issue and one of the leading causes of maternal mortality. The significantly increased incidence of 0.12-3.7% of eclampsia reported in African countries versus 0.04-0.12% in various European studies may be due to the complex nature of the disease, which is more suitable for a specialized and multi-disciplinary team, often unavailable to most patients in developing countries[1,6-8]. Multiple risk factors are known for the development of preeclampsia, including primiparity, maternal age over 40 years, chronic hypertension or diabetes, multiple gestations, and a prior history of preeclampsia[9]. However, risk factors for the progression to eclampsia are much less clear. The most frequent premonitory signs of eclampsia occurrence are severe hypertension, headaches, ankle clonus, epigastric or right upper quadrant pain, and visual disturbances. However, analysis was not performed on these signs to determine if they constituted statistically significant risk factors for the development of eclampsia in patients already diagnosed with severe preeclampsia, and the degree of hypertension does not appear to consistently predict the risk of eclampsia[10]. Therefore, it is imperative to understand other signs and symptoms that may indicate that a patient is at a higher risk for developing eclampsia. In the current study, numerous putative risk factors for eclampsia in patients with severe preeclampsia and positive NSS were identified, particularly a lack of adequate prenatal care, severe hypertension, and signs of HELLP (H for hemolysis) syndrome, which should be addressed to prevent the development of dangerous seizures and reduce both maternal and fetal morbidity and mortality. Most studies to date detail the risk factors for the development of preeclampsia, rather than the development of eclampsia from pre-eclamptic patient cohorts[11,12]. In one study, the risk factors for developing eclampsia were similar to those of developing preeclampsia, which included low maternal age, primiparity, obesity, short duration of marriage prior to pregnancy, low level of education, history of preeclampsia, and inadequate prenatal care[13]. In our study, all of the above-mentioned risk factors that were analyzed were found to be significant in the univariate analysis. However, only inadequate prenatal care was found to be a significant risk factor upon multivariate analysis. This discrepancy is most likely due to our comparison of patients with severe preeclampsia and patients with eclampsia, rather than analyzing the difference between patients with eclampsia and non-complicated pregnancies.

Table 1. Patient characteristics on admission

	Eclampsia (%)	Severe preeclampsia + NSS (%)
Maternal age		
≤25 years	59 (42.8)	75 (27.6)
26-34 years	55 (39.8)	108 (39.7)
≥35 years	24 (17.4)	89 (32.7)
Gestational age		
<34 weeks	14 (10.0)	16 (5.9)
34-36 weeks	38 (27.5)	84 (30.9)
≥37 weeks	86 (62.5)	172 (63.2)
GCS		
15	55 (39.9)	272 (100)
9-14	65 (47.1)	0
≤8	18 (13.0)	0
SBP		
≥160 mmHg	119 (86.2)	186 (68.4)
140-159	19 (13.8)	72 (26.5)
<140	0	14 (5.1)
DBP		
≥110	13 (9.4)	10 (3.7)
90-110	121 (87.7)	256 (94.1)
<90	4 (2.9)	6 (2.2)
Edema		
Generalized	31 (22.5)	24 (8.8)
Lower extremities	101 (73.2)	234 (86.0)
Absent	6 (4.3)	14 (5.2)
Proteinuria (traces on urine test strip)		
1+	40 (29.0)	55 (20.2)
2+	43 (31.2)	101 (37.1)
≥3+	55 (39.8)	34 (12.5)
Diuresis		
<500 mL/24 hrs	22 (15.9)	34 (12.5)
≥500 mL/24 hrs	116 (84.1)	238 (87.5)
Symptoms		
Nausea & vomiting	104 (75.4)	202 (74.3)
Jaundice	6 (4.3)	5 (1.8)
Epigastric pain	48 (34.8)	75 (27.6)
Hemoglobin		
≥12 g/dL	30 (21.7)	89 (32.7)
7-12 g/dL	99 (71.8)	175 (64.4)
<7 g/dL	9 (6.5)	8 (2.9)
Hematocrit		
≥35%	88 (63.8)	126 (53.6)
<35%	50 (36.2)	146 (46.4)
Platelets (10^3/mm^3)		
≥100	103 (74.6)	257 (94.5)
50-99	27 (19.6)	13 (4.8)
<50	8 (5.8)	2 (0.7)
PTT		
Normal	90 (65.2)	174 (64.0)
Long	48 (34.8)	98 (36.0)
AST		
<70 UI/L	83 (60.1)	205 (75.4)
≥70 UI/L	55 (39.9)	67 (24.6)
Bilirubin		
<12 mg/dL	78 (56.5)	165 (60.7)
≥12 mg/dL	60 (43.5)	107 (39.3)
Creatinine		
≤100 µmol/L	100 (72.5)	237 (87.0)
>100 µmol/L	38 (27.5)	38 (13.0)
Ultrasound	n=37	n=54
Placental abruption	5 (13.9)	6 (11.1)
Oligohydramnios	12 (32.4)	18 (33.3)
Intrauterine growth restriction	13 (35.1)	14 (25.9)
Fetal demise	4 (10.8)	6 (11.1)
Complications		
Retroplacental hematoma	16 (11.6)	29 (10.7)
Acute renal insufficiency	37 (26.8)	35 (12.9)
Acute pulmonary edema	9 (6.5)	17 (6.3)
Mortality		
Deceased	19 (13.8)	21 (7.7)
APGAR score	n=93	n=258
≥7	60 (64.5)	192 (74.4)
4-6	14 (15.1)	23 (8.9)
≤3	17 (18.3)	40 (15.5)
Fetal complications		
Prematurity	52 (37.7)	100 (36.7
Intrauterine growth restriction	35 (25.4)	54 (19.9)
Fetal demise	11 (8.0)	24 (8.8)
Method of delivery		
Cesarean	108 (78.3)	175 (64.3)
Vaginal	30 (21.7)	97 (35.7)

GCS: Glascow Coma score, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, PTT: Partial thromboplastin time, AST: Asparate aminotransferase, NSS: Neurosensory signs

Table 2. Univariate and multivariate analysis of potential risk factors for the development of eclampsia in patients admitted for severe preeclampsia and positive neurosensory signs

		Univariate analysis			Multivariate analysis	
Variable		χ^2	p	OR (95% CI)	p	OR (95% CI)
Maternal age (years)	≤25	9.589	**0.002**	1.962 (1.277-3.014)	0.139	1.559 (0.866-2.807)
	26-34					
	≥35					
Gestational age (weeks)	≤33	2.453	0.117	0.554 (0.262-1.170)		
	34-36					
	≥37					
Parity	Primiparous	6.388	**0.011**	1.708 (1.126-2.591)	0.068	0.551 (0.291-1.044)
	Pauciparous					
	Multiparous					
Pre-partum care	Followed					
	Not followed	11.622	**0.001**	2.84 (1.53-5.26)	**<0.001**	8.966 (3.909-20.563)
Systolic blood pressure (mmHg)	<140					
	140-160					
	≥160	15.311	**<0.001**	2.896 (1.675-5.007)	**0.008**	3.130 (1.342-7.305)
Diastolic blood pressure (mmHg)	<90					
	90-110					
	≥110	5.704	**0.017**	2.896 (1.675-5.007)		
Edema	Lower extremities					
	Generalized	14.665	**<0.001**	2.90 (1.678-5.342)	0.088	2.064 (0.897-4.752)
	Absent					
Proteinuria	1x					
	2x					
	≥3x	294	0.588	0.891 (0.587-1.352)		
Diuresis (mL/hrs)	<500	0.920	0.338	1.328 (0.743-1.915)		
Digestive symptoms	Nausea/ Vomiting	0.058	0.809	0.943 (0.588-1.514)		
	Icterus	2.208	0.137	2.427 (0.826-4.342)		
	Epigastric pain	2.266	0.132	0.714 (0.460-1.108)		
Hemoglobin (g/dL)	<7					
	7-12					
	≥12	5.359	**0.021**	0.571 (0.354-0.921)		
Hematocrit (%)	≥35					
	<35	11.166	**0.001**	2.050 (1.160-3.620)	0.211	1.479 (0.801-2.730)
Platelets (10^3/mm^3)	<50	12.571	**<0.001**	16.677 (2.06-135)	**0.027**	13.106 (1.344-127.823)
	50-99					
	≥100					

Table 2. Continued

Prothrombin time (%)	<50	0.185	0.667	0.756 (0.210-2.723)		
	50-69					
	≥70					
PTT	Normal					
	Prolonged	0.062	0.803	0.947 (0.617-1.454)		
AST (UI/L)	<70					
	≥70	10.150	**0.001**	2.028 (1.308-3.143)	**0.007**	3.575 (1.313-9.736)
Bilirubin-emia (mg/dL)	<12					
	≥12	0.650	0.420	1.186 (0.783-1.797)		
Creatinine (µmol/L)	≤100					
	>100	13.460	**<0.001**	2.573 (1.537-4.308)	0.427	0.728 (0.333-1.592)
HELLP syndrome	ELLP	19.145	**<0.001**	5.245 (2.332-11.798)	**<0.001**	5.828 (2.439-13.925)
Prematurity		0.033	0.856	1.040 (0.681-1.588)		
Fetal growth restriction		3.559	0.590	1.635 (0.979-2.732)		
Oligohy-dramnios		1.928	0.165	0.706 (0.431-1.156)		
Fetal demise		0.000	0.998	0.999 (0.469-2.129)		
Delivery mode	Vaginal					
	Cesarean	8.300	**0.004**	1.995 (1.242-3.207)		

PTT: Partial thromboplastin time, AST: Asparate aminotransferase, CI: Confidence interval, OR: Odds ratio, HELLP: Hemolysis elevated liver enzyme levels, and low platelet levels, ELLP: Elevated liver enzyme levels, and low platelet levels

It is imperative to be able to identify which patients are at risk of progressing from preeclampsia to eclampsia to initiate preventative measures. In 2011, the Preeclampsia Integrated Estimate of Risk (fullPIERS) model was developed for predicting complications in patients admitted for preeclampsia. This model demonstrated good discriminatory and stratification abilities and has been both internally and externally validated[14-17]. However, the fullPIERS model was designed for use in high-resource settings. In line with this, another model was required for use in low-resource settings that could be easily implemented by mid-level local health care workers because a majority of deaths assigned to disorders of pregnancy occur in low and middle income countries (LMICs), where there is a high incidence of delay in identification of high-risk patients, transportation, and administration of appropriate treatment[18-20]. Thus, the miniPIERS was developed for use in LMICs. Due to the frequent lack of laboratory data in rural settings, the miniPIERS is based solely on patient demographics, signs, and symptoms. Using a recommended cut-off at 15% for risk of probability of adverse outcome to initiate closer follow-up, and 25% as the cut-off for referral to a tertiary care facility, the miniPIERS has the potential to significantly improve patient care in resource-limited settings[18]. However, both the fullPIERS and miniPIERS models were designed to identify patients who are most at risk for developing any complications, not only eclampsia. Therefore, more work must be done to better stratify those at risk and identify which patients have the highest risk of developing eclampsia to begin the proper, specific preventative measures. The goal of early detection of preeclampsia is to be able to introduce effective preventative treatment during pregnancy to avoid eclamptic seizures and their subsequent complications. Indeed, prenatal care has been shown to play an important role in the incidence of eclampsia and other complications of pregnancy, and the lack of proper prenatal care for pregnant women is a major public health concern both in Morocco, as well as other developing countries, where management of high-risk patients is limited, making it challenging to detect early warning signs and act on modifiable risk factors[21-24]. In our work, 89.9% of the patients with eclampsia and 75.7% of the control group were not properly followed prior to admission, conveying a 9 times increased risk of developing eclampsia. This is an important factor to address as there are reliable algorithms published for the calculation of risk of preeclampsia that may be beneficial in the early identification of these patients. As discussed above, one potential intervention for addressing this issue is the implementation

of the regular use of the miniPIERS assessment in community healthcare settings. By training community workers to identify the risk factors of the miniPIERS model and use the formula or application to calculate the predicted risk of complications, at-risk patients may be identified earlier and sent to the proper higher-level care facilities. Hypertension is one of the defining characteristics of preeclampsia and severe hypertension with a systolic BP greater than 160 mmHg has been viewed as a warning sign of evolution to eclampsia[10]. Based on a recent systematic review of reports of patients with eclampsia, it is unclear whether the degree of hypertension is consistently related to eclampsia[10]. However, the results of the present study demonstrate that severe hypertension is a risk factor for the development of seizures in patients with preeclampsia, and therefore should be taken as a sign of condition severity. HELLP syndrome, described for the first time by Weinsteinen in 1982, is the acronym for HELLP. It is generally considered to be a subset of preeclampsia[25,26]. Although the laboratory thresholds used to define HELLP syndrome are not unanimous, Sibai proposed the following definition in order to be able to combine and compare the various studies in the literature: hemolysis defined as at least two of the following: 1) lactate dehydrogenase >600 IU/L; 2) presence of schistocytes or; 3) total bilirubinemia >12 mg/L. Additionally, the author defined elevated liver enzymes as AST >70 IU/L and low platelets as a platelet count below 100.000/mm^3[27,28]. In the present work, bilirubin was the only laboratory value that could be found relating to hemolysis, so the diagnosis of hemolysis, and thus HELLP syndrome, could not be formally made. Therefore, the analysis was performed based on previously described incomplete HELLP syndrome parameters, defined as elevated liver enzymes (EL), ELLP (EL and thrombocytopenia), and isolated low platelet count (LP). On multivariate analysis, AST >70 IU/L, LP (platelet count of 50.000-100.000/mm^3 and <50.000/mm^3) and ELLP were found to be independent predictors of eclampsia in this specific patient population. These results are in line with those previously published, which found a statistically significant association between HELLP syndrome and eclampsia, with a 15-25% incidence of HELLP syndrome reported in patients with eclampsia in various studies[13,16,29]. The limitations of this study lie chiefly in the methodology: due to the nature of the retrospective chart review, various important data points were missing from our data set, including reliable indicators for hemolysis, the time between the onset of symptoms and admission to our facility, and the severity of the disease upon admission at upstream facilities. Each patient included in the series was given magnesium sulfate, introducing a possible confounding factor as to who may have developed eclampsia in the natural course of the disease. Additionally, some blood tests reported were performed after the onset of eclamptic seizures, introducing possible bias in those data as well. Finally, the inclusion criteria used for this study may have affected the outcome of the analyses because both the case and control patients had severe, late-stage presentation of the disease. This may account for some of the discrepancies between our results and previously published data.

Conclusion

Eclampsia is a serious public health concern, especially in LMICs where access to proper prenatal care and screening are often not available. It is important to identify risk factors that may increase the probability of patients with severe preeclampsia progressing to eclampsia. We report several major risk factors in the development of eclampsia, including inadequate prenatal care, severe hypertension, and incomplete HELLP syndrome. Thus, it is imperative to address access to care for all pregnant patients, especially in developing countries, treat hypertension early, and to be aware of the importance of incomplete HELLP syndrome to improve maternal and fetal outcomes and work to prevent this devastating condition.

Ethics

Ethics Committee Approval: The study was approved by the Medical School of Marrakech Local Ethics and Scientific Committee, a committee that is in the set-up stage so till now we do not have an approval number.
Informed Consent: This is a retrospective study and data were old, de-identified and anonymized, then we did not need consents.
Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.R., M.E.S., Y.F., A.R.EA., Concept: H.R., A.R.EA., Design: H.R., Y.F., A.R.EA., Data Collection or Processing: H.R., Y.F., Analysis or Interpretation: H.R., Y.F., M.E.S., A.R.EA., Literature Search: H.R., M.E.S., Writing: H.R., M.E.S.
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Ykl-40 and cancer antigen 72-4 as new and promising diagnostic and prognostic markers for endometrial cancer

Endometriyal kanser için yeni ve umut verici tanı ve prognostik belirteçler olarak YKL-40 ve kanser antijen 72-4

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Abstract

Objective: To determine the predictive role of serum levels of YKL-40 and cancer antigen (CA) 72-4 in the diagnosis of endometrial cancer (EC).
Materials and Methods: Forty-one patients with EC and 21 women with uterine polyps were evaluated between January and December 2015 in a prospective study.
Results: Age, body mass index, preoperative serum YKL-40 and CA 72-4 levels were significantly higher in the malignant group compared with the control group. Serum YKL-40 levels were significantly higher in patients with superficial myometrial invasion and no lymph node involvement (p=0.042; p=0.004). No relationship between clinicopathologic factors and serum CA 72-4 levels was found.
Conclusion: Serum CA 72-4 and YKL-40 levels are increased in women with EC compared with uterine polyps. Preoperative serum YKL-40 levels may be associated with favorable prognostic factors. The determination of YKL-40 before surgery may be helpful in the evaluation of the regional lymph nodes.
Keywords: YKL-40, cancer antigen 72-4, endometrial cancer, screening

Öz

Amaç: Endometrial kanser (EC) tanısında YKL-40 ve kanser antijen (CA) 72-4 serum düzeylerinin prediktif rolünü belirlemektir.
Gereç ve Yöntemler: Ocak-Aralık 2015 tarihleri arasında EC tanısı almış 41 hasta ve uterin polip tanısı almış 21 olgu prospektif olarak değerlendirildi.
Bulgular: Yaş, vücut kitle indeksi, preoperatif serum YKL-40 ve CA 72-4 düzeyleri kontrol grubuna göre malign grupta anlamlı olarak yüksek bulundu. Serum YKL-40 düzeyleri, yüzeyel myometrial invazyonlu ve lenf nodu tutulumu olmayan olgularda anlamlı olarak yüksek saptandı (p=0,042; p=0,004). Klinikopatolojik faktörler ile serum CA 72-4 düzeyleri arasında ilişki bulunamadı.
Sonuç: EC'li hastalarda serum CA 72-4 ve YKL-40 düzeyleri uterin polip saptanmış olgulara kıyasla artmıştır. Preoperatif serum YKL-40 seviyeleri, uygun prognostik faktörlerle ilişkili olabilir. YKL-40'ın cerrahi öncesi saptanması, bölgesel lenf nodlarının değerlendirilmesinde yardımcı olabilir.
Anahtar Kelimeler: YKL-40, kanser antijen 72-4, endometriyum kanseri, tarama

PRECIS: Serum YKL-40 and CA 72-4 may be used in the prediction of endometrial cancer

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Introduction

Abnormal uterine bleeding is the initial symptom in 75 to 90% of the patients with endometrial carcinoma (EC). Most EC (80%) is diagnosed at stage 1 and five-year survival rates exceed 95%. A significant portion of patients have recurrent or advanced disease at admission and outcome is poor in these patients. In patients with regional spread, five-year survival rates are about 68% and if there is distant disease, five-year survival rates drop to 17%[1].

In recent years, tumor markers have been widely investigated in order to detect EC during early phases and to monitor the disease. Numerous tumor markers have been studied for this purpose. Nevertheless, there are currently no markers routinely used in the diagnosis of the EC. Cancer antigen (CA)-125 has been reported to be high in 19% to 40% of patients with EC[2,3]. Sood et al.[4] found that high serum CA-125 levels were strongly associated with the prediction of extrauterine disease and high mortality. However, CA-125 values do not seem to be useful in the early diagnosis of the EC. Serum human epididymis protein (HE)-4 levels were significantly higher in patients with recurrent EC. Furthermore, HE-4 was likely to be superior to CA-125 in detecting recurrent EC[5]. Both of these markers are significantly correlated with higher histologic grade, stage, lymph node metastases, myometrial invasion, and cervical involvement in patients with EC[6-8].YKL-40 (Human Chitinase-3-like protein 1) is a glycoprotein that belongs to the chitinase family. Its exact function is not yet clearly known. High serum levels of YKL-40 are associated with extracellular matrix breakdown and angiogenesis[9]. Elevated serum YKL-40 levels have been reported in certain cancer types such as breast cancer, colorectal cancer, lung cancer, glioma, leukemia, melanoma, and some diseases including hepatic fibrosis, osteoarthritis and rheumatoid arthritis[10-17]. CA 72-4, a human tumor-associated glycoprotein (TAG), is frequently used as a tumor marker for diagnosing and predicting prognosis in gastric and ovarian cancers[18,19]. CA72-4 TAG-72 is not affected by pregnancy or the menstrual cycle phase, and it is barely influenced by inflammatory conditions[19,20]. In this study, our objective was to determine the efficacy of YKL-40 and CA72-4 in the early diagnosis of EC and to evaluate whether both markers had prognostic value for EC.

Materials and Methods

Study population

The study was performed in İstanbul University Cerrahpaşa Faculty of Medicine, Department of Gynecology and Obstetrics, Division of Gynecologic Oncology between January and December 2015. The study was approved by the Ethics Committee of İstanbul University Cerrahpaşa Faculty of Medicine (approval number: 83045809/604.01/02-46067). Approval of the local ethics committee was provided and the study protocol adhered to the principles of the Declaration of Helsinki. Informed written consent for participation in the study was obtained from all women. The manuscript was prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement[21].The exclusion criteria were defined as presence of one of the following conditions: (i) a suspicious secondary malignancy, (ii) systemic disease such as renal and/or hepatic failure, congestive heart failure, chronic respiratory disease, (iii) neoadjuvant chemotherapy, (iv) history of chemotherapy or radiotherapy for any malignancy, (v) history of endometriosis, and (vi) major intraperitoneal disease (e.g., Crohn's disease, ulcerative colitis).The inclusion criteria in the study and control groups were as follows: 27 women with menometrorrhagia or postmenopausal bleeding who underwent saline infusion sonography and had a pre-diagnosis of endometrial polyp in our clinic (internal) were enrolled. Blood samples were taken shortly before the endometrial biopsy in all women with the pre-diagnosis endometrial polyps. The histologic diagnosis was confirmed as endometrial polyps in 21 women, and these patients made-up our control group. Two women had proliferative endometrium and four women had EC. The women with EC were included in the study group. All patients with endometrial polyps underwent hysteroscopic resection. Thirty-seven women who underwent endometrial biopsy in an external center and were diagnosed as having EC were enrolled in the study. Blood samples were taken shortly before surgery in all women with a diagnosis of EC. The laparoscopic or laparotomic operations were performed in our clinic. Surgical staging included total hysterectomy, bilateral salpingo-oophorectomy, pelvic lymphadenectomy, and para-aortic lymphadenectomy, if necessary. A total of 41 women (4 internal + 37 external) with EC and 21 women with endometrial polyps were included in the statistical analysis.

All histopathologic diagnoses were made by two gynecologic pathologists. Histologic type and stage of the disease according to International Federation of Gynaecology and Obstetrics were available in all patients with EC[22]. The charts and pathologic findings were reviewed in a blinded fashion, without knowing the preoperative serum YKL-40 and CA 72-4 values.

Biochemical analysis

Blood samples were collected in ethylenediamine tetraacetic acid (EDTA)-containing tubes and anticoagulant-free tubes after an overnight fast. Plasma and serum were separated immediately and stored at -80 °C until required for analysis.

Measurement of serum YKL-40 concentrations

Serum YKL-40 concentrations were determined using a commercial enzyme-linked immunosorbent assay (ELISA) kit with a double-antibody sandwich enzyme immunoassay technique [Human Chitinase-3-like protein 1 (YKL-40, CHI3L1)] ELISA Kit, Cat. No. YHB0684Hu; Shanghai Yehua

Biological Technology Co. Ltd, China). Each ELISA analysis was carried out according to the manufacturer's instructions. All tests showed intra- and inter-assay coefficients of variations (CVs) below 8% (n=15) and 10%, respectively. The analytical sensitivity of the test was 0.52 ng/mL.

Measurement of serum cancer antigen 72-4 concentrations

Serum CA 72-4 concentrations were determined using a commercial ELISA kit with a quantitative competitive enzyme immunoassay technique [CA724 (CA724) BioAssay™ ELISA Kit (Human), Cat. No. 184403; Biomol GmbH; Waidmannstr. 35; 22769 Hamburg; Germany]. Each ELISA analysis was carried out in accordance with the manufacturer's instructions. All tests showed intra- and inter-assay CVs below 7% (n=15) and 9% (n=15), respectively. The analytical sensitivity of the test was 0.1 ng/mL. Biochemical parameters and tumor markers were analyzed using routine methods with commercial kits and autoanalyzer.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 16.0 software package (SPSS Inc., Chicago, IL, USA), and clinicopathologic variables, including the categorical data, were analyzed using the chi-square or Fisher's exact test. Mean values were compared between the groups using the independent Samples t-test and one-way analysis of variance (ANOVA) test. All reported confidence interval values were calculated at the 95% level. A probability (p) value of less than 0.05 was defined as statistically significant.

Results

Some of the clinicopathologic data of the study population are summarized in Table 1. The mean age of the subjects in the malignant group was 60.27 (range, 39-82) years and 45.29 (range, 27-70) years in control group. The age of the patients, body mass index, preoperative serum YKL-40 and CA 72-4 levels were significantly higher in the malignant group compared with the control group (Figures 1, 2). In all patients, serum YKL-40 and CA72-4 levels were higher in postmenopausal compared with premenopausal patients. YKL-40 and CA 72-4 levels in premenopausal and postmenopausal patients were 88.4±60.4 ng/mL and 129.9±79.3 ng/mL (p=0.023), and 5.9±5.5 U/mL and 8.56±4.6 U/mL (p=0.047), respectively. Among patients with EC, 36 (87.8%) had endometrioid and 5 (12.2%) had serous histopathologic type. The distribution of surgical stages was as follows: 63.4% in stage 1, 22% in stage 2, 9.7% in stage 3, and 4.9% in stage 4. Histologic grades were found as grade 1 in 24.4%, grade 2 in 53.7%, and grade 3 in 21.9% of the patients with EC. Twenty-five and 16 patients underwent laparotomic and laparoscopic staging surgery, respectively. Systematic pelvic lymphadenectomy was performed in all patients, and para-aortic lymphadenectomy was performed in 11 (27%) patients.

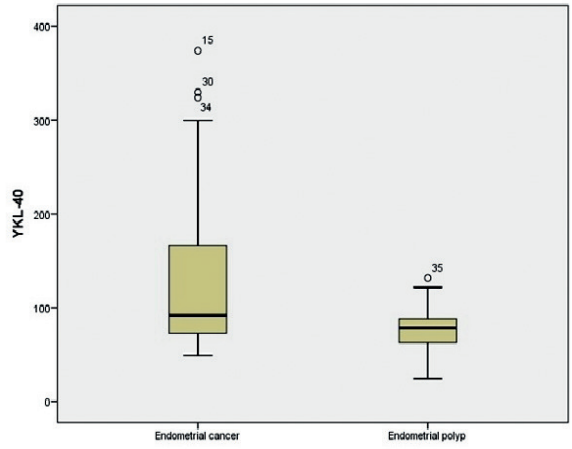

Figure 1. Preoperative serum YKL-40 concentrations in endometrial cancer and endometrial polyps

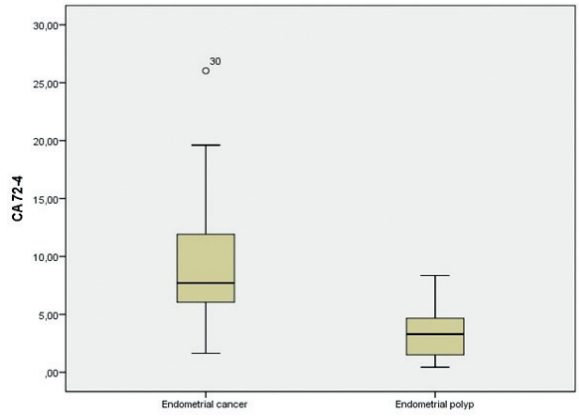

Figure 2. Preoperative serum cancer antigen 72-4 concentrations in endometrial cancer and endometrial polyps

CA 72-4: Cancer antigen 72-4

The median numbers of pelvic and para-aortic lymph nodes removed were 20.48±9.4 (range, 10-46) and 10.55±6 (range, 6-23), respectively. Postoperative adjuvant treatment was administered to 28 (69%) patients. Intracavitary radiotherapy was given to all patients who needed adjuvant treatment, and external beam radiotherapy was given to 42.8%. Seven patients who had stage 3-4 disease or serous-type cancer also received adjuvant chemotherapy. Older age, advanced stage disease, serous histopathologic type, high grade, deep myometrial invasion, cervical stromal involvement, and lymph node involvement were associated with lower serum YKL-40 levels (Table 2). Serum YKL-40 levels were significantly higher in patients with superficial myometrial invasion and no lymph node involvement (p=0.042; p=0.004). No relationship between clinicopathologic factors and serum CA 72-4 levels was found (Table 2). Receiver operating characteristics curve analyses for YKL-40 and CA 72-4 are shown in Figure 3. The area under the curve was 0.893, and 0.659 for CA 72-4 and YKL-40, respectively. A cut-off value of 4.13 U/mL for

Table 1. Clinical features and postoperative histopathologic findings of all patients (n=62)

	Endometrial cancer (n=41)	Endometrial polyps (n=21)	p value
Age, mean± SD (range)	60.27±12 (39-82)	45.29±9.9 (27-70)	**<0.001***
BMI (kg/m^2), mean± SD (range)	30.4±4.8(21-43)	25.4±2.6(20-35)	**<0.001***
Gravida, mean± SD	3.51±2.5	3.3±2.3	0.798*
Parity, mean± SD	2.73±1.9	2.33±1.8	0.455*
Preoperative serum YKL-40, mean± SD (ng/mL)	128.93±84.6	78.4±25.6	**0.001***
Preoperative serum CA 72-4, mean± SD (U/mL)	9.38±5.2	3.58±2.21	**<0.001***
Preoperative serum CA-125, mean± SD (U/mL)	75.46±243.5	26.2±18.2	0.360*
	n (%)		
Menopausal status			
Premenopausal (n=27)	10 (24.4)	17 (81)	**<0.001**†
Postmenopausal (n=35)	31 (75.6)	4 (19)	
Surgery type			
Laparoscopy	16 (39)	NA	**
Laparotomy	25 (61)	NA	
FIGO postoperative stage of disease			
IA	19 (46.3)	NA	
IB	7 (17.1)	NA	
II	9 (22)	NA	
IIIA	1 (2.4)	NA	
IIIB	1 (2.4)	NA	**
IIIC1	2 (4.9)	NA	
IV	2 (4.9)	NA	
Histologic type			
Endometrioid	36 (87.8)	NA	**
Serous	5 (12.2)	NA	
Histologic grade			
I	10 (24.4)	NA	
II	22 (53.7)	NA	**
III	9 (21.9)	NA	
Myometrial invasion			
None	5 (12.2)	NA	
≤1/2	20 (48.8)	NA	**
>1/2	16 (39)	NA	
Tumor size in endometrial cavity			
≤2 cm	9 (22)	NA	**
>2 cm	32 (78)	NA	
Cervical stromal involvement			
Absent	30 (73)	NA	**
Present	11 (27)	NA	
LVSI			
Absent	26(63.4)	NA	**
Present	15 (36.6)	NA	

Table 1. Continued

Pelvic lymphadenectomy	41 (100)	NA	**
Para-aortic lymphadenectomy	11 (27)	NA	**
Number of removed pelvic nodes, mean ± SD (range)	20.48±9.4 (10-46)	NA	**
Number of removed para-aortic nodes, mean± SD (range)	10.55±6 (6-23)	NA	**
Adjuvant treatment			
No	13 (31)	NA	
Yes	28 (69)	NA	
EBRT+ICRT	9 (32.1)		**
ICRT	12 (42.9)		
ICRT+CT	4 (14.3)		
EBRT+ICRT+CT	3 (10.7)		

BMI: Body mass index, FIGO: International Federation of Gynecology and Obstetrics, NA: Not applicable, LVSI: Lymphovascular space invasion, EBRT: External beam radiotherapy, ICRT: Intracavitary radiotherapy, CT: Chemotherapy, SD: Standard deviation, CA: Cancer antigen
*: Independent samples t-test, †: Chi-square test, **: Could not be calculated, Bold indicates statistical significance

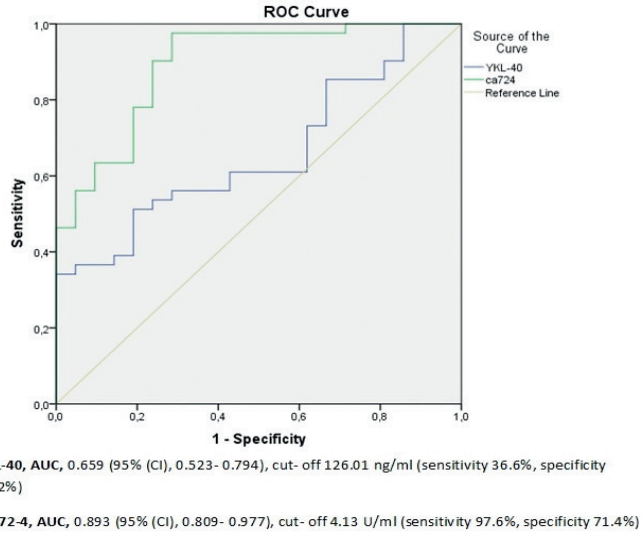

Figure 3. Comparison of ROC curves for YKL-40 and cancer antigen72-4 in the distinction of endometrial polyps from endometrial cancer

CA 72-4: Cancer antigen 72-4, CI: Confidence interval

CA 72-4 revealed 97.6% sensitivity, 71.4% specificity, 87% positive predictive value (PPV) and 93.8% negative predictive value (NPV). A cut-off value of 126.01 ng/mL for YKL-40 revealed 36.6% sensitivity, 95.2% specificity, 93.8% PPV and 43.5% NPV. The positive likelihood ratiowas 7.6 and 3.4 for YKL-40 and CA 72-4, respectively (Table 3).

Discussion

The incidence of EC has been on the rise during recent years. Although the majority of cases are diagnosed early, survival rates in advanced stages are likely to be lower. Tumor markers that could be used in early diagnosis of the EC have been investigated in the literature[23]. However, there is no evidence for the clinical usefulness of serum tumor markers for routine use in EC screening. CA-125 has been reported to be elevated in 19% to 40% of patients with EC[2,3]. Serum HE-4 levels were significantly higher in recurrent EC and superior to CA-125 levels in detecting recurrent EC[5]. CA-125 and HE-4 are significantly correlated with histologic grade, stage, lymph node metastases, myometrial invasion, and cervical involvement in EC[6,8]. However, CA-125 and HE-4 values are not useful in the diagnosis of early-stage EC. Some studies reported that serum YKL-40 levels were higher in patients with EC compared with healthy individuals[24,25]. Fan et al.[24] suggested that, serum YKL-40 had advantages over CA-125 in the diagnosis of early-stage EC, contributing to early management of the disease. Serum YKL-40 levels are also associated with early stage[24]. Diefenbach et al.[26] found no statistically significant association of YKL-40 with patient age, tumor grade, histology or stage. The authors claimed that this finding was helpful in the identification of high-risk subsets of patients with worse clinical outcomes[26]. In another study, there was no significant difference in terms of the stage and grade of the tumor and for prognostic factors between malignant and benign groups[27]. However, YKL-40 was significantly higher in non-endometrioid-type cancer than in endometrioid-type. A recent meta-analysis by Cheng et al.[28] evaluated 234 patients with EC and 300 controls. This meta-analysis concluded that YKL-40 had a moderately high diagnostic accuracy, with a sensitivity of 0.74, a specificity of 0.87 and on the basis of their meta-analysis, therefore, circulating YKL-40 could be promising and meaningful in the diagnosis of EC. In the present study, preoperative serum YKL-40 levels were significantly higher in the malignant group compared with the benign group. Preoperative serum YKL-40 levels were found to be lower in patients with older age, advanced stage, serous type, high

grade, deep myometrial invasion, cervical stromal involvement, and lymph node involvement. Serum YKL-40 levels were significantly higher in patients with superficial myometrial invasion and no lymph node involvement (p=0.042). Preoperative serum YKL-40 levels may be associated with favorable prognostic factors. CA72-4 is commonly used as a tumor marker for diagnosing and predicting outcomes in gastric and ovarian cancers[18,19]. Anastasi et al.[29] evaluated the

Table 2. The relationship between YKL-40 and cancer antigen 72-4 results with clinicopathologic factors in the endometrial cancer group (n=41)

	YKL-40 mean ± SD (ng/mL)	p value	CA 72-4 mean ± SD (U/mL)	p value
Age at diagnosis				
<60 (n=22)	139.59±88.6	0.37*	10.36±6.1	0.175*
>60 (n=19)	115.53±80		7.21±3.2	
Menopausal status				
Premenopausal (n=10)	113.8±91.4	0.536*	10±6.7	0.448*
Postmenopausal (n=31)	133.16±83.2		8.55±4.7	
FIGO stage				
I-II (n=35)	132.7±87.7	0.499*	9.13±5.4	0.469*
III-IV (n=6)	107.1±66.1		10.81±3.8	
FIGO stage				
I (n=26)	133.62±92.6		9.08±5.6	
II (n=9)	128.11±76	0.663†	7.56±4.7	0.806†
III (n=4)	126.25±75		10.75±4.6	
IV (n=2)	67±12.7		9±0	
Histologic type				
Endometrioid (n=36)	129.56±89.2	0.824*	8.72±5.4	0.557*
Serous (n=5)	120.4±40.7		10.2±3	
Histologic grade				
I (n=10)	136±95.6	0.877†	9.8±4.7	0.532†
II (n=22)	130±92.5		8.05±5.9	
III (n=9)	116.22±52.4		10±3.4	
Myometrial invasion				
≤1/2 (n=25)	155.36±97.3	0.042*	9.96±6.1	0.247*
>1/2 (n=16)	86.38±28.3		7.25±2.6	
Tumor size in endometrial cavity				
≤2 cm (n=9)	97.11±55.7	0.212*	8.89±3.7	0.993*
>2 cm (n=32)	137.25±89.7		8.91±5.6	
LVSI				
Absent (n=26)	128.72±87.9	0.984*	8.55±4.7	0.180*
Present (n=15)	129.30±81.6		10.81±5.8	
Cervical stromal involvement				
Absent (n=30)	132.01±90	0.706*	9.68±5.5	0.541*
Present (n=11)	120.5±70		8.55±4.4	
Lymph node involvement				
Absent (n=37)	143.4±94.9	0.004*	9.58±5.9	0.400*
Present (n=4)	77.04±27.4		7.49±2.4	

FIGO: International Federation of Gynecology and Obstetrics, LVSI: Lymphovascular space invasion, SD: Standard deviation, CA: Cancer antigen
*: Independent-samples t-test, †: ANOVA; Bold indicates statistical significance, p<0.05 is statistically significant

Table 3. Sensitivity and speciŞcity of YKL-40 and cancer antigen 72-4 in the study groups

+LR	Cut-off	Sensitivity	Specificity	PPV	NPV	
YKL-40 (ng/mL)	126.01	36.6	95.2	93.8	43.5	7.6
CA 72-4 (U/mL)	4.13	97.6	71.4	87.0	93.8	3.4

PPV: Positive predictive value, NPV: Negative predictive value, LR: Likelihood ratio, CA: Cancer antigen

CA72-4 values among patients with ovarian cancer (71.0%) and patients with endometriosis (13.8%). They concluded that CA72-4 determination could be useful to confirm the benign nature of ovarian endometriomas in women with high CA-125 levels[29]. Serum CA72-4 levels were significantly related with cancer cell lymph node metastasis in pancreatic and gastric cancers[30,31]. There are a limited number of studies about the role of CA 72-4 in the diagnosis and prognosis of EC. Regarding this issue, Gadducci et al.[32] demonstrated that serum CA 72-4 levels were raised in approximately 22-32% of the cases in patients with EC. In contrast, Moore et al.[33] found that when compared with control levels, there was no statistically significant difference when comparing serum CA 72-4 levels in all EC stages combined or in stage 1 cancers alone. Soper et al.[34] found that, CA 72-4 levels were elevated (higher than 6 U/mL) in 4% of patients with localized disease and 30% with metastasis. Hareyama et al.[35] reported that serum CA72-4 was increased above the cut-off value in 31.9% of patients with EC. They also found that serum CA72-4 positivity (values >4 IU/mL) was correlated with depth of myometrial invasion, adnexal metastasis, lymphovascular space involvement, and pelvic and para-aortic lymph node metastasis. Hareyama et al.[35] suggested that measuring serum concentrations of CA 72-4 could be useful for predicting and monitoring the progression of disease. Myriokefalitaki et al.[36] investigated the potential additional prognostic benefit of preoperative CA 72-4 level in 282 patients with EC. In this retrospective study, they found that increased CA 72-4 values were statistically significantly correlated with advancing disease stage, which was shorter disease-free survival and higher recurrence rate, hence CA 72-4 appears to be reliable predictor of poor prognosis in patients with EC[36]. In our study, preoperative serum CA 72-4 levels were significantly higher in malignant group, compared to benign group. No relationship was found between clinicopathologic factors and serum CA 72-4 levels. Serum CA 72-4 levels had a sensitivity of 97.6%, which demonstrates its sufficiency to distinguish endometrial polyps from EC. The limitations of this study are the low number of patients in the study and control groups.

Conclusion

The results obtained from our study suggest that measurements of CA 72-4 levels can help differentiate EC from endometrial polyps. Preoperative levels of CA 72-4 can be used as a marker in the early diagnosis of EC. Preoperative serum YKL-40 levels may be associated with favorable prognostic factors. Further prospective studies using large populations and randomized clinical trials are needed to clarify the impact of YKL-40 and CA 72-4 on the definitive diagnosis and prognosis of EC and, eventually, to distinguish benign and malignant endometrial tumors.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of İstanbul University Cerrahpaşa Faculty of Medicine (approval number: 83045809/604.01/02-46067).

Informed Consent: Informed written consent for participation in the study was obtained from all women.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Design: V.S., F.D., O.G., H.U., Data Collection or Processing: S.K., N.S., Analysis or Interpretation: S.K., F.D., T.B., M.A., Writing: V.S, İ.K, O.G.

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

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Use of clomiphene citrate alone, urinary follicle-stimulating hormone alone, or both combined sequentially in patients with unexplained subfertility undergoing intrauterine insemination: A randomized trial

Sadece klomifen sitrat, sadece üriner folikül stimülan hormon ve her ikisinin kombinasyonu ile intrauterin aşılama yapılan açıklanamayan infertilitesi olan hastalarda kullanımı: Randomize çalışma

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Abstract

Objective: To compare the successes of clomiphene citrate (CC) alone, pure human urinary follicle-stimulating hormone (uFSH) alone, and both combined sequentially in patients with unexplained subfertility couples undergoing intrauterine insemination (IUI).

Materials and Methods: Patients aged 18-38 years who had a normal uterine cavity, at least one normal fallopian tube, and regular menses and were unable to conceive despite unprotected intercourse for at least 12 months were randomized to receive CC alone, uFSH alone, or sequential CC and uFSH before a single IUI. The primary outcomes were clinical pregnancy and live birth rates. The study was approved by the ethics committee of our institution.

Results: A total of 135 patients were randomized, and 121 of these were able to complete the study. Of these, 30% (n=36) had CC alone, 34% (n=41) had uFSH alone, and 36% (n=44) had sequential CC and uFSH. The three groups did not significantly differ in terms of age, duration of infertility, hormone levels, and semen parameters. For CC alone, uFSH alone, and sequential CC plus uFSH groups, pregnancy rates were 8.3%, 17.1%, and 18.2%, respectively (p>0.05), and live birth rates were 8.3%, 12.1%, and 13.6%, respectively (p>0.05).

Conclusion: In women with unexplained infertility, use of uFSH seemed to increase the success rate compared with CC alone. The sequential regime can significantly reduce the treatment cost if gonadotropin/IUI cycles are planned.

Keywords: Clomiphene citrate, urinary follicle-stimulating hormone, intrauterine inseminaton, unexplained subfertility

Öz

Amaç: Açıklanamayan infertilitesi olan çiftlerde intrauterin inseminasyon (IUI) sırasında klomifen sitratın (CC), üriner foliküler stimülan hormonun (uFSH) tek başına ve kombine CC ve uFSH kullanımı başarısının karşılaştırılması.

Gereç ve Yöntemler: On sekiz - otuz sekiz yaş arasında, normal uterin kaviteye ve en az bir fallop tüpünün normal olduğu, düzenli menstrülel siklusa sahip, 12 aylık korunmasız ilişki sonrası gebe kalamayan hastalar IUI öncesinde sadece CC, uFSH ve CC ardından uFSH verilmesi için randomize edilmiştir. Primer sonuçlar klinik gebelik ve canlı doğumlar olarak belirlenmiştir. Bu çalışma hastanenin etik komitesi tarafından onaylanmıştır.

Bulgular: Yüz otuz beş hasta randomize edildi, 121 hasta çalışmayı tamamlayabildi. Bu hastaların %30'una (n=36) sadece CC, %34'üne (n=41) sadece uFSH ve %36'sı (n=44) ardışık CC ve uFSH verildi. Bu üç grup yaş, infertilite süresi, hormon seviyeleri ve semen parametreleri açısından istatistiksel olarak farklı değildi. Sadece CC, uFSH ve ardışık CC ve uFSH grubunda sırasıyla gebelik oranları %8,3, %17,1, ve %18,2 (p>0,05) ve canlı gebelik oranları %8,3, %12,1,ve %13,6 (p>0,05) olarak saptandı.

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Sonuç: Açıklanamayan infertilitesi olan kadınlarda uFSH kullanımı yalnız CC kullanımına göre daha yüksek başarı oranlarına sahiptir. Ardışık rejim uygulanması gonadotropin uygulanan IUI sikluslarındaki maliyeti azaltmaktadır.
Anahtar Kelimeler: Klomifen sitrat, üriner foliküler stimülan hormon, intauterin tohumlama, açıklanamayan subfertilite

PRECIS: Administration of clomiphene citrate for 5 days appears reasonable in reducing the treatment cost for couples with unexplained subfertility who undergo gonadotropin/intrauterine insemination cycles.

Introduction

Intrauterine insemination (IUI) following ovarian stimulation (OS) is a reasonable treatment modality in cases of unexplained subfertility, which is responsible for approximately 10-30% of infertility causes[1-3]. This approach will possibly maintain its place in the management of unexplained subfertility in the near future unless the cost of assisted reproductive technology (ART) is reduced to an acceptable level for most couples. Ideal OS treatment before IUI procedures is expected to minimize the likelihood of ovarian hyperstimulation and multiple pregnancies while increasing chance of live birth (LB) rates[4,5]. Although various empiric OS regimes exist to improve a couple's chance of conceiving, a great deal of debate regarding the superiority of one regime over another has continued over the years[6]. Therefore, randomized studies are needed to address ongoing controversy and guide use in regard with the choice of treatment regimen. Clomiphene citrate (CC) and gonadotropin are well-established agents to induce follicular development. CC is commonly used as the initial agent for OS as it has certain advantages such as being affordable, patient friendly and well-tolerated, and does not require frequent monitoring. Women who remain anovulatory on CC or who have not conceived after several cycles are considered appropriate candidates for OS with gonadotropins. However, gonadotropin has higher cost compared with CC and requires multiple injections[7]. These disadvantages have raised a quest for alternative treatment protocols. For this purpose, a sequential CC/gonadotropin regimen has been considered as a potential alternative to reduce both treatment cost and gonadotropin dose used if IUI is planned[8]. We conducted this randomized trial to compare CC alone, pure human urinary follicle-stimulating hormone (uFSH) alone or both combined sequentially for OS followed by IUI in patients with unexplained subfertility of at least 12 months.

Materials and Methods

This randomized trial included couples with unexplained subfertility who presented to the reproductive endocrinology and infertility clinic at Zeynep Kamil Training and Research Hospital, from January 2009 to March 2011. The ethics committee at our institution approved this study (approval number: 18145/07.12.2010). Each participant provided informed consent.

Study population

For this study, diagnosis of unexplained subfertility was made after a standard infertility examination (including semen analysis, hysterosalpingogram and ovulation test) resulted in normal findings in couples who could not conceive despite unprotected intercourse for at least 12 months. On this basis, all male partners had a normal semen analysis and all female partners had at least one healthy fallopian tube, normal uterine cavity, and regular menses. To minimize heterogeneity and confounding factors in the study population, the following criteria were considered as the exclusion reasons: age of less than 18 or more than 38 years, secondary infertility, body mass index (BMI) above 30 kg/m^2 or below 19 kg/m^2, basal (day 3) FSH levels ≥14 IU/L, irreregular menses, any endocrine diseases, or history of use of gonadotropin, oral contraceptives or other hormonal drugs during the last 6 months.

Patient evaluation

All participants were evaluated using a standard approach. On the second or third day of the menstrual period, transvaginal ultrasound (TVU) using a 6.5-MHz probe (Logic alfa 200 GE Medical A/S Milwaukee, United States) was performed to evaluate uterus size, endometrial thickness, adnexa and ovaries as well as count the number of antral follicles. The following hormonal and biochemical tests were obtained on the same day; estradiol (E_2), FSH, luteinizing hormone (LH), prolactin, thyroid function tests, fasting blood sugar, and renal and liver function tests. Hysterosalpingography (HSG) was performed for the assessment of tubal patency after menstruation according to the literature-based recommendations, followed by laparoscopy if HSG was inconclusive. The standard evaluation also included age, BMI, duration of infertility, blood pressure, pelvic examination, cervical smear, vaginal-cervical cultures, and infection screening if needed. For the evaluation of male fertility, our andrology laboratory evaluated all semen samples using the World Health Organization and Kruger criteria[9,10]. The following parameters of semen analysis were accepted as the inclusion criteria: a concentration more than 15 million/mL, type A plus B motility higher than 40% and normal morphology more than 14%. Sperm preparation was performed soon after ejaculation based on swim up technique using Earle's Balanced Salt (Sigma) and *in vitro* fertilization-30 (Vitrolife) (Merck Company) solutions.

Study groups

An OS protocol coupled with IUI was the treatment of choice offered to couples diagnosed with unexplained infertility following the required gynecologic and laboratory evaluations. The study population was stratified into three groups; CC alone, uFSH alone, and combination of CC and uFSH (CC-uFSH). The first, second, and third study participant was included in the CC alone, uFSH alone, and sequential CC-uFSH groups, respectively, and this allocation sequence was followed until each group contained 45 patients (a total of 135 women).

Treatment protocols

All the patients had a TVU assessment on the second or third day of the cycle. A CC dosage of 100 mg/day orally was initiated in the CC alone and sequential CC-uFSH groups, and an uFSH dose of 75 IU subcutaneously in the uFSH alone group. After a treatment course of five consecutive days, a follow-up TVU was performed in all patients. Afterwards, the CC alone group received no additional treatments, the sequential CC-uFSH group started administering daily uFSH injections with a dose of 75 IU as a sequential treatment, and the uFSH alone group continued the treatment protocol already being used. TVU monitoring was performed in all patients to check follicle growth at certain intervals until the day of human chorionic gonadotropin (hCG) injection, when the lead follicle reached ≥18 mm in the CC alone group and ≥17 mm in the uFSH alone and sequential CC-uFSH groups, which was followed by a single IUI procedure at around 36-40 hours after subcutaneous hCG injection (10.000 IU). The patients rested for 10 min following the IUI. No medications were used in the luteal phase. Criteria for cycle cancellation were as follows; spontaneous ovulation before the day of hCG, inadequate response to CC, and excessive response to uFSH or CC.

Outcomes

The primary outcomes were clinically detectable gestation (CDG) and LB rates. CDG was defined as an intrauterine pregnancy with a positive heart beat detected by TVU at approximately six weeks of gestation. LB was defined as delivery of a living infant after 24 completed weeks of gestation. The secondary outcomes were miscarriage rates, endometrial thickness, number of dominant follicles, duration of treatment, and number of uFSH injections used. Miscarriage was defined as loss of a clinically detectable pregnancy before 20 weeks of gestation. Endometrial thickness (distance between both endometrial-myometrial junctions in sagittal plane 1 cm below the uterine fundus) measured on the day of hCG was used in the comparisons. These outcomes were compared among the three groups.

Statistical Analysis

Data were analyzed using NCSS (Number Cruncher Statistical System) 2007 & Power Analysis and Sample Size 2008 (Utah, USA). One-way analyses of variance (ANOVA), Pearson's chi-square, and the Student's t-test were the statistical tests used for the comparisons. A p value of 0.05 was accepted as the cut-off for statistical significant. All values are given as mean ± standard deviation or percentage.

Results

A total of 150 women met the inclusion criteria of the study; 15 women declined to participate in the study. The remaining 135 women were randomized to a treatment group according to the sequence of clinical appointment, and 121 of those were able to complete the study. Of the 121 patients, 30% (n=36) had CC alone, 34% (n=41) had uFSH alone, and 36% (n=44) had sequential CC-uFSH (Figure 1). The rate of treatment cancellation was 2.2%, 6.6%, and 4.4% in the CC alone, uFSH alone, sequential CC-uFSH groups, respectively (p>0.05). The three groups did not significantly differ in terms of age, duration of infertility and basal FSH, LH, and E_2 (Table 1). The groups also showed no statistical difference in the semen parameters (p>0.05, Table 2). Table 3 displays the outcomes of the treatment protocols. The duration of treatment was shorter in the CC alone group than in the uFSH alone or sequential CC-uFSH group (p<0.01), but there

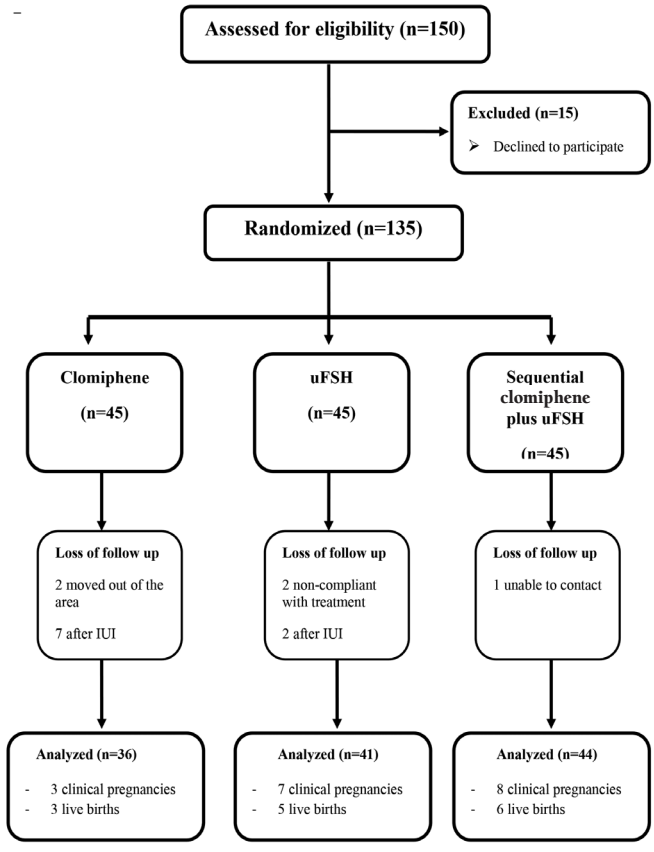

Figure 1. Flowchart of the study

uFSH: Urinary follicle-stimulating hormone, IUI: Intrauterine insemination

was no difference between the uFSH alone and sequential CC-uFSH groups. The consumption of uFSH was less in patients who took sequential CC-uFSH than in those who took uFSH alone (p<0.01). The number of mature follicle differed between the groups (p<0.01). The sequential CC-uFSH group had the highest number of mature follicle on the day of hCG. Endometrial thickness did not differ between the three treatment regimens (p>0.05). For the CC alone, uFSH alone, and sequential CC-uFSH groups, CDG were 8.3%, 17.1%, and 18.2%, respectively. LB rates were 8.3%, 12.1%, and 13.6%, respectively. The CC alone group had lower CDG and LB rates than the other groups, but this did not show statistical difference (p>0.05, Table 3). The rates of CDG and LB were quite similar between the uFSH alone and sequential CC-uFSH groups (Table 3). No miscarriage occurred in the CC group. On the other hand, miscarriage occurred in two

Table 1. Comparison of patient characteristics between the groups

	CC alone (n=36)	uFSH alone (n=41)	Sequential CC+uFSH (n=44)	p
Age (years)*	29.3±5.8	27.9±4.4	28.1±4.1	>0.05
Duration of infertility (years)*	4.7±5.4	4.1±2.2	4.5±6.2	>0.05
Cycle day 3 FSH (mIU/mL)*	6.8±2.6	6.6±1.9	7.8±5.9	>0.05
Cycle day 3 LH (mIU/mL)*	5.2±1.9	5.6±2.8	5.1±2.7	>0.05
Cycle day 3 E2 (pg/mL)*	56.3±58.4	50.6±38.3	53.1±41.6	>0.05
Unilateral tubal obstruction**	5.6	14.6	15.9	>0.05

*One-way ANOVA test and **Chi-square test were used for the statistical analysis
CC: Clomiphene tedavide ilk kullanılan ajanlardan bir tanesidir. uFSH: Urinary follicle-stimulating hormone, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, E_2: Estradiol
Values were given mean ± standard deviation or percentage

Table 2. Comparison of sperm parameters between the groups

	CC alone (n=36)	uFSH alone (n=41)	Group 3q CC + uFSHq (n=44)	p
Total number of sperm (million)	97.1±54.9	91.4±78.1	110.4±83.7	>0.05
Total motility (%)	69.3±23.2	80.1±17.2	75.9±17.8	>0.05
Volume (mL)	2.9±0.9	3.1±1.2	3.1±1.3	>0.05
Normal morphology (%)	27.1±26.9	21.9±26.9	33.7±32.3	>0.05

One-way ANOVA test was used for the statistical analysis.
CC: Clomiphene tedavide ilk kullanılan ajanlardan bir tanesidir. uFSH: Urinary follicle-stimulating hormone
Values were given mean ± standard deviation or percentage

Table 3. Comparison of the outcomes between the groups

	CC alone (n=36)	uFSH alone (n=41)	Sequential CC + uFSH (n=44)	p
Duration of treatment (days)	5±0	8.6±2.8	9.3±3.1	<0.01
Number of uFSH injections used		8.3±3.3	4.7±2.7	<0.01
Number of follicle	1.6±0.9	2.1±1.1	3.2±1.1	<0.01
Endometrial thickness (mm)	7.7±2.1	8.4±1.9	8.3±2.1	>0.05
Clinical pregnancy	8.3 (3)	17.1 (7)	18.2 (8)	>0.05
Live birth	8.3 (3)	12.1 (5)	13.6 (6)	>0.05

*One-way ANOVA test, **Student's t-test, and ***Chi-square test were used for the statistical analysis
CC: Clomiphene tedavide ilk kullanılan ajanlardan bir tanesidir. uFSH: Urinary follicle-stimulating hormone
Values were given mean ± standard deviation or percentage

of seven patients in the uFSH alone group and two of eight patients in the sequential CC-uFSH group; the miscarriage rates did not differ between these groups (p>0.05).

Discussion

This randomized study provides the outcomes of couples with unexplained subfertility who underwent one session of IUI following OS with CC alone, uFSH alone, or sequential CC-uFSH. Based on our results, use of uFSH alone or sequential CC-uFSH as an OS protocol seemed to offer higher success rates compared with CC alone, although the difference was not significant. The sequential protocol had similar CDG and LB rates to uFSH alone. Although the sequential regimen increased the success rate compared with CC alone regimen, it reduced the number of uFSH injections used for OS compared with uFSH alone. Thus, the treatment cost could be estimated to be lower in the sequential regimen than in the uFSH alone regimen, without affecting the duration of treatment and success rate.

Although it is inconclusive as to whether ongoing pregnancy rates are higher with IUI (with or without OS) than in timely sexual intercourse according to the most recent Cochrane analysis[11], clinical practice usually agrees on the use of oral agents or gonadotropin in IUI cycles to presumably improve the chance of conceiving in the presence of unexplained subfertility[12]. In a randomized study of 93 unexplained infertile patients who had a trial of OS/IUI, Berker et al.[12] found that the rate of ongoing pregnancy was 11.6% (5/43) and 18% (9/50) when treatment regimen was CC and FSH, respectively. Dankert et al.[13] showed that LB rates were respectively 31.4% and 30.3% in the CC and FSH groups among a total of 138 patients (68 couples with unexplained infertility, 70 couples with male subfertility) who underwent IUI up to four cycles. These studies did not reach statistical significance in the aforementioned outcomes, as with our study. In a comparison of two drugs, Diamond et al.[14] reported that CC and gonadotropin groups had LB rates of 32.2% and 23.3% in a high number of patients with unexplained infertility who underwent OS/IUI for up to four cycles, respectively, and this difference achieved statistical significance. The patient populations and treatment protocols used in these studies were quite similar to our patient population. However, we think that a similar success rate was also able to be achieved with a sequential CC-uFSH regimen based on our results. Therefore, it may be reasonable to use CC priming to reduce the treatment cost before administrating gonadotropin. In a retrospective analysis of 648 IUI cycles, Ryan et al.[15] revealed less cost and multiple pregnancies in a sequential oral medication (CC or letrozole or tamoxifen) and human menopausal gonadotropin (hMG) group than in an hMG alone group, with similar success rates in both groups. A recent metaanalysis including 22 studies showed use of CC to reduce FSH consumption during OS, with no change in clinical and LB rates [RR (relative risk), 1.0, (95% CI (confidence interval), 0.8-1.4) and RR, 0.9 (95% CI, 0.6-1.2) respectively][16]. Endometrial thickness and pattern are considered to affect the success of IUI[17]. CC may cause adverse effects on endometrial quality due to its anti-estrogenic effects. Despite no statistical difference, the mean endometrial thickness was greater in the uFSH alone and sequential CC-uFSH groups than in the CC alone group in our study. This may show a benefit of using gonadotropin following CC because the success rates were similar in both the uFSH alone and sequential CC-uFSH groups, but lower in the CC alone group than in the others. Therefore, a sequential protocol may offer an advantage by correcting the possible adverse effects of CC on the endometrium.

There are some limitations in this study. First, the sample size was not large enough to draw definitive conclusions. Second, because the study did not have an expectant management group as a control group, the contribution of treatment protocols to clinical pregnancy or LB rates remained unclear. Last, the mean duration of infertility was relatively long because couples with unexplained infertility should undergo IUI procedure for at least two trials to be eligible for the use of ART in Turkey if they have insurance funded by the government to cover treatment expenses. The main strength of this study was its randomized design.

Conclusion

In women with unexplained infertility, although clinical pregnancy and LB rates for IUI with CC, uFSH or sequential CC-uFSH did not reach statistical significance, use of uFSH seemed to increase the success rate compared with use of CC alone. Use of CC for 5-days before gonadotropin can significantly reduce the treatment cost if gonadotropin/IUI cycles are planned.

Ethics

Ethics Committee Approval: Zeynep Kamil Training and Research Hospital, from January 2009 to March 2011. The ethics committee at our institution approved this study (approval number: 18145/07.12.2010).

Informed Consent: Each participant provided informed consent.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Design: M.R.A., S.A., Data Collection or Processing: R.A., M.R.A., Analysis or Interpretation: M.R.A., Literature Search: R.A., Writing: R.A.

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

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A surgical technique for secondary repair of obstetric anal sphincter injuries; sphinctero-vagino-perineoplasty

Obstetrik anal sfinkter hasarının sekonder onarımında cerrahi teknik; sfinktero-vajino-perineoplasti

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Abstract

Objective: This study was conducted to present the preliminary results of seven patients treated with sphinctero-vagino-perineoplasty for secondary repair of obstetric anal sphincter injuries.

Materials and Methods: This retrospective study was conducted on the records of seven patients who underwent secondary repair of obstetric anal sphincter injuries at the colorectal surgery unit of a tertiary care center between February 2015 and December 2017.

Results: All patients with solid stool incontinence were fully recovered at postoperative month 3. The Wexner incontinence score was significantly improved (decreased from 14.12 [range: 8-20] to 2.28 [range: 1-4]). The complication rate was 85.7% (wound infection, abscess, hematoma, detachment).

Conclusion: Combined repair of anal sphinchters, perineal body, superficial transverse perineal muscles, and bulbospongious muscles, which contribute to anal continence, may improve surgical outcomes in patients with obstetric anal sphincter injuries.

Keywords: Anal incontinence, obstetric anal sphincter injury, perineoplasty, sphincteroplasty, vaginoplasty

Öz

Amaç: Bu çalışma obstetrik anal sfikter hasarının sekonder onarımında sfinktero-vajino-perineoplasti uygulanan yedi hastanın erken dönem sonuçlarını bildirmek amacıyla yapıldı.

Gereç ve Yöntemler: Obstetrik anal sfikter hasarı nedeniyle sekonder onarım planlanan ve Şubat 2015-Aralık 2017 tarihleri arasında bir üniversite hastanesinin kolorektal cerrahi ünitesinde sfinktero-vajino-perineoplasti uygulanan yedi hastanın kayıtları geriye dönük incelendi.

Bulgular: Postoperatif 3. ayda hiçbir hastada katı gaita inkontinansı gözlenmedi. Wexner inkontinans skorunda belirgin düzelme (14,12'den [aralık: 8-20] 2,28'e [aralık: 1-4] geriledi) izlendi. Hastaların %85,7'sinde komplikasyon (infeksiyon, abse, hematom, detaşman) gelişti.

Sonuç: Anal kontinansı oluşturan yapıların (anal sfinkterler, perineal body, süperfisyal transvers perineal kaslar, bulbospongiosus kaslar) kombine onarımı obstetrik anal sfinkter hasarının sekonder onarımında daha iyi sonuçlar edilmesine imkan sağlayabilir.

Anahtar Kelimeler: Anal inkontinans, obstetrik anal sfinkter hasarı, perineoplasti, sfinkteroplasti, vajinoplasti

Introduction

The most common cause of anal incontinence in women is obstetric anal sphincter injuries (OASIS). Clinically apparent OASIS occur in less than 3 percent of vaginal deliveries[1]. In spite of primary repair, up to 5% of these patients develop anal incontinence, which severely impairs their quality of life[2,3]. When OASIS is treated for anal incontinence, it is considered as a secondary repair even if no primary repair has been performed during the postpartum period[4]. There is no consensus on which surgical technique is

PRECIS: We present the preliminary results of seven patients treated with sphinctero-vagino-perineoplasty for secondary repair of OASIS.

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effective for secondary repair of OASIS[5]. Unfortunately, long-term consequences of surgical interventions (sphincteroplasty, perineorrhaphy, and transposition of muscle flaps) are unsatisfactory. All of these techniques are focused on either isolated anal sphincter repair, or reconstruction of tissue supporting the anal canal with the anal sphincter unrepaired. We believe that the damage to the perineal body, superficial transverse perineal muscles, and bulbospongiosus muscles, which provide contribution to anal continence, is ignored, especially in direct surgical repair. Therefore, the success rates of conventional techniques focused on anal sphincter repair for OASIS are low. In this study, we present the preliminary results of a surgical technique that involves combined restoration of vaginal, perineal, and anal sphincter muscles, for secondary repair of OASIS.

Materials and Methods

The medical records of 7 women who underwent secondary repair of OASIS at a colorectal surgery unit of a tertiary care center between February 2015 and December 2017 were reviewed. Prior to the surgery, endoanal ultrasonography (EAUS) was performed to measure the degree of sphincter defect. Wexner incontinence scores (WIS) were recorded in both the preoperative and postoperative periods. Postoperative complications and follow-up periods were also recorded. The menstrual cycle was taken into account. Progesterone supplements were given to delay menstruation in the postoperative period. Sexual intercourse was prohibited for 3 months postoperatively.

Surgical technique

All patients underwent surgery in the lithotomy position under spinal anesthesia. First, a semicircular incision was made matching the projection of the anal sphincter. The second U-shaped incision was made on the posterior commissure of the bulbospongiosus muscles (Figure 1). The vaginal mucosa was dissected to a depth of 6 cm, extending laterally to the bulbospongiosus and puborectal muscles and inferiorly to the perineal body. The anorectal mucosa was dissected from the sphincter muscles at a depth of 5 cm. The anal sphincters were dissected free with at least a depth of 4 cm (Figure 2). The retracted ends of the sphincters were identified and repaired using the overlapping method using 3/0 polydioxanone sutures. The perineal body was formed on the external anal sphincter (EAS) and the anus was centralized by end-to-end repair of the free ends of the bulbospongiosus muscles (Figure 3). A subcutaneous Penrose drain was placed. Anoderm, vagina, and perineal skin were sutured with absorbable materials. V-Y advancement flaps were used in patients with tissue defects between the vagina and anus (Figure 4). Protective ileostomy was performed only in cases where tissue loss of the anal canal and vagina (cloaca-like deformity) were noticed.

Figure 1. A semicircular incision matched the projection of the bulbospongiosus muscles

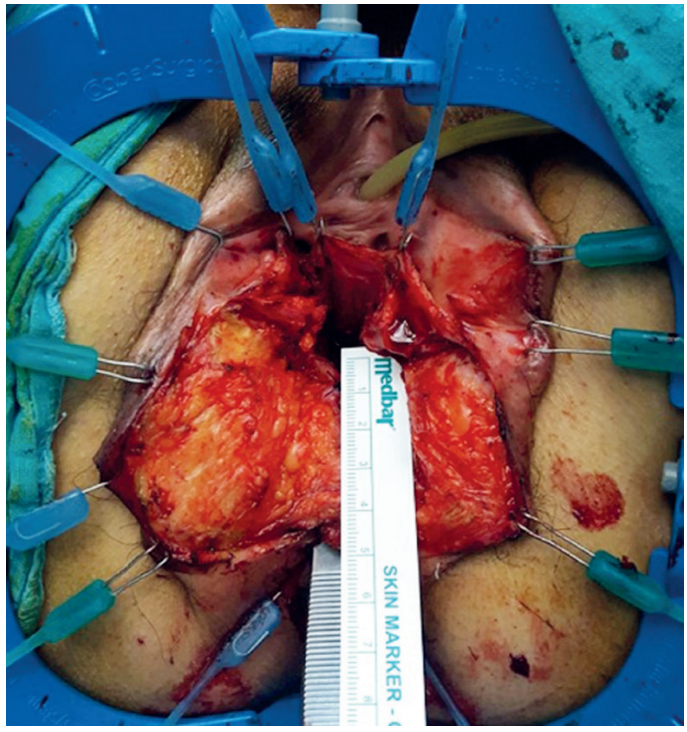

Figure 2. The vaginal mucosa was dissected at a depth of 6 cm, extending laterally to the bulbospongiosus and puborectal muscles and inferiorly to the perineal body. The anorectal mucosa was dissected from the sphincter muscles at a depth of 5 cm. The anal sphincters were dissected free with at least a depth of 4 cm

Statistical Analysis

Statistical Package for the Social Sciences 17.0 for Windows Data was used. Descriptive frequencies were applied.

This study was conducted according to the principles of the 1975 Helsinki Declaration, which was revised in 2000. Informed consent was obtained from patients.

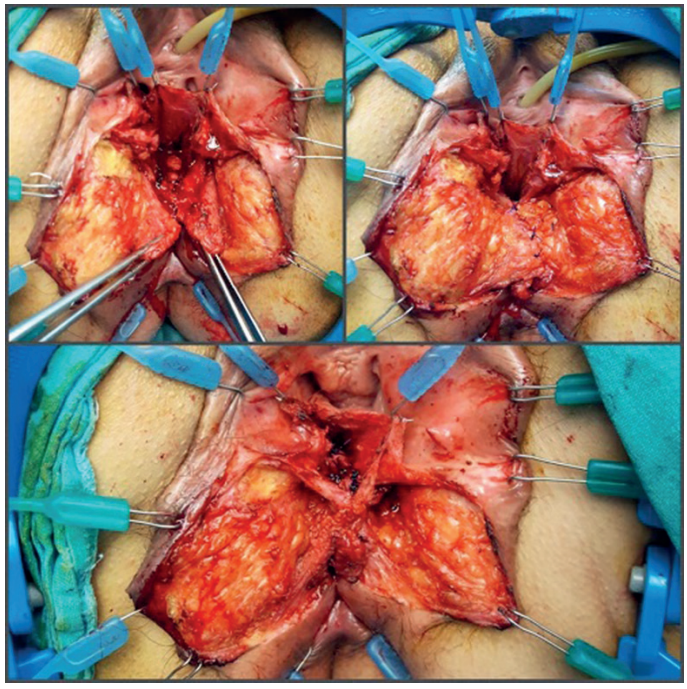

Figure 3. The retracted ends of the sphincters were repaired using the overlapping method. The perineal body was formed on EAS and the anus was centralized through end-to-end repair of the free ends of the bulbospongiosus muscles.

The study was approved by the İnönü University Local Ethics Committee (approval number: 2017/12-6). Informed consent forms were completed by all participants.

Results

The average age of the women was 34.85 (range, 23-42) years, the average parturition number was 3.14 (range, 1-7), and the mean body mass index (BMI) was 27.14 (range, 22.7-30.4) kg/m^2. All patients had a history of vaginal delivery. They developed symptoms of anal incontinence immediately after their first vaginal birth, and gradually worsened in the following births. The mean duration of symptoms was 39.4 (range, 6-120) months. EAUS showed both complete defect of EAS and complete and/or partial defect of the internal anal sphincter (IAS) in 6 patients. There was EAS defect only in one patient. The anal sphincter defect angle did not exceed 130 degrees in any patient. One patient reported incontinence to gas and liquid, and six patients reported incontinence to solid stool, liquid, and gas (Table 1). All six patients with solid stool incontinence were fully recovered at postoperative month 3. The mean preoperative WIS was 14.42 (range, 8-20), whereas it was 2.28 (range, 1-4) at postoperative month 3. The postoperative complications (wound infection, abscess, detachment, hematoma) developed in 6 patients (85.7%). V-Y advancement flaps were used in two of these patients, and free skin flap transfer was performed in one patient. The

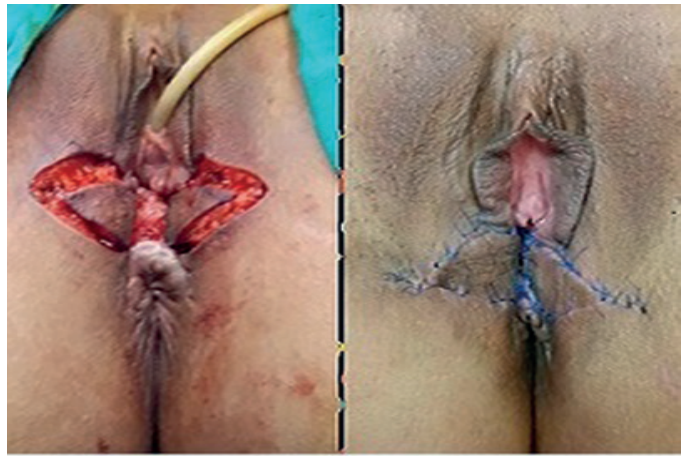

Figure 4. V-Y advancement flap between the vagina and the anus

average follow-up duration was 12.28 (range, 3-26) months.

Discussion

There are no randomized controlled trials comparing primary and secondary repair of OASIS due to ethical obstacles[6]. Based on observational studies, results of primary repair, especially performed by experienced surgeons, are superior to secondary repair[7,8]. Direct techniques include reconstruction of the sphincter itself, either by end-to-end or overlapping methods[9,10]. Indirect techniques include reconstruction of striated muscles or fasciae surrounding anal canal, and transposition of a striated muscle flap[11-13]. In the literature, surgical techniques are focused primarily on isolated anal sphincter repair[9,10,14,15]. Although short-term results of sphincteroplasty are satisfactory with 75-86% improvement in incontinence, they attenuate with time notifying that less than 50 percent of patients are still continent after 5-10 years[16]. The retraction of sphincters and overlooked pudendal injury may predispose to failure in sphincteroplasty[15,17,18]. Indirect methods in which anal sphincters remain unrepaired have poor functional results. The muscles supporting the anal canal necessitate conscious voluntary effort, so it is difficult to maintain continence for prolonged periods, and impossible during sleep[17]. As a result, the success rates of conventional surgical techniques decrease with time after surgery[19-21]. All of these techniques are focused on either isolated anal sphincter repair, or reconstruction of tissue supporting the anal canal without anal sphincter repair. We believe that the damage to the perineal body, superficial transverse perineal muscles, and bulbosupongiosus muscles, which provide contribution to anal continence, is ignored, especially in direct surgical repair. In the present study, all patients with solid stool incontinence were fully recovered at postoperative month 3. The improvement in WIS was statistically significant. Although complications were high they were resolved properly. We performed diverting colostomy in only two patients because diverting colostomy was not obligatory

Table 1. The characteristics of patients

Characteristics	p1	p2	p3	p4	p5	p6	p7
Age	23	37	42	39	35	38	30
BMI	24	27.5	31.2	27	22.7	30.4	27.2
Number of vaginal births	1	2	4	6	2	4	1
Time interval since the first vaginal birth [months (m)/years (y)]	6 m	8 y	19 y	16 y	13 y	25 y	5 y
Duration of symptoms (month)	6	12	120	6	12	60	60
Preoperative WIS	8/20	16/20	17/20	14/20	13/20	20/20	13/20
Postoperative WIS (at 3rd month)	1/20	2/20	1/20	3/20	2/20	3/20	4/20
Complications							
Wound infection	+	+	-	+	+	+	+
Abscess	-	-	-	-	+	+	+
Hematoma	-	-	-	-	+	-	-
Detachment	+	+	-	+	+	+	+
Diverting ostomy	-	-	+	-	-	+	-
V-Y advancement flap transfer	+	-	-	-	+	-	-
Free skin flap transfer	-	-	-	-	-	+	-

BMI: Body mass index WIS: Wexner incontinence scores

in the treatment of OASIS. Venkatesh et al.[22] also reported favorable results of combined surgery in 44 patients with traumatic cloaca, the majority of which were secondary to obstetric injuries. They used puborectalis interposition, sphincteroplasty and perineal body repair. All patients except five, had regained both fecal and gas continence. Five women also improved following biofeedback therapy. Anaraki et al.[23] performed sphincteroplasty and perineoplasty with skin advancement flap to reform the perineal body in 19 women with traumatic cloacal defects. Significant improvement in FI scores (decreased from 12.7 to 2.6), quality of life (increased from mean of 45 to 95), dyspareunia (decreased from mean of 5 to 0.8) and sexual function satisfaction (increased from mean score of 0.2 to 4.7) in these patients encouraged them to recommend this technique as an effective surgical method. Their complication rate was 15.7% (wound infection in 2 patients, rectovaginal fistula in one patient), which was managed conservatively. In the current study, although the FI score was significantly improved (decreased from 14.12 to 2.28), the complication rate was higher (85.7%).

Conclusion

Although the small sample size and absence of long-term results were limitations of this study, the satisfactory preliminary results encourage us to consider that combined repair of anal sphincters, perineal body, superficial transverse perinei muscles, and bulbospongiosus muscles may improve surgical outcomes in patients with OASIS.

Ethics

Ethics Committee Approval: The study was approved by the İnönü University Local Ethics Committee (approval number: 2017/12-6).

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.A., A.D., Concept: A.Ş., M.A., A.D., D. Ö., Design: A.Ş., M.A., A.D., D.Ö., Data Collection or Processing: A.Ş, M.A., Analysis or Interpretation: A.Ş, M.A., A.D., D.Ö, Literature Search: A.Ş., Writing: A.Ş.

Conflict of Interest: There is no conflict of interest.

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Maternal platelet-to-lymphocyte ratio at delivery can predict poor neonatal outcome in preterm births

Doğumda maternal platelet-lenfosit oranı preterm doğumlarda kötü neonatal sonlanımları öngörebilir

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Abstract

Objective: To determine the role of the platelet-to-lymphocyte ratio (PLR) in predicting poor neonatal outcome among preterm births (PTB).
Materials and Methods: The medical records of 439 PTBs and 200 normal pregnancies were reviewed retrospectively using some personal and obstetric data, as well as complete blood count reports.
Results: There were significantly poor neonatal outcomes among PTBs in regard to birth weight, APGAR score, morbidity, and mortality. There were significantly poor outcomes for preterm neonates delivered to mothers with PLR ≥80 at delivery for low APGAR score, respiratory distress syndrome, intraventricular hemorrhage and perinatal death. There was a significant negative correlation between maternal PLR at delivery and birth weight, as well as gestational age of PTB.
Conclusion: Maternal PLR at delivery has a significant relationship with neonatal outcomes. It can predict preterm neonates with poor outcomes.
Keywords: Lymphocytes, neonatal, outcome, platelets, preterm, ratio

Öz

Amaç: Preterm doğumlar (PTD) arasında kötü neonatal sonlanımları öngörme açısından platelet-lenfosit oranının (PLO) rolünü belirlemektir.
Gereç ve Yöntemler: Dört yüz otuz dokuz PTD ve 200 normal gebeliğin tıbbi kayıtları, bazı kişisel ve obstetrik veriler ile tam kan sayımı raporları kullanılarak retrospektif olarak incelendi.
Bulgular: PTD'ler arasında; doğum ağırlığı, APGAR skoru, morbidite ve mortalite açısından anlamlı derecede kötü neonatal sonlanımlar vardı. Doğum sırasında PLO ≥80 olan annelerin dünyaya getirdiği preterm yenidoğanlarda, düşük APGAR skoru, respiratuar distres sendromu, intraventiküler kanama ve perinatal ölüm açısından anlamlı kötü sonuçlar elde edildi. Doğum sırasındaki maternal PLO ile doğum ağırlığı ve PTD gestasyonel yaşı arasında anlamlı negatif korelasyon vardı.
Sonuç: Doğumdaki maternal PLO'nun neonatal sonlanımlar ile anlamlı bir ilişkisi bulunmaktadır. Bu şekilde kötü sonlanımlı preterm yenidoğanlar öngörülebilir.
Anahtar Kelimeler: Lenfosit, neonatal, sonlanım, platelet, preterm, oran

Introduction

Premature birth continues to be one of the most important challenges of modern obstetrics through its high incidence and its implications on neonatal morbidity and mortality[(1)]. Preterm birth (PTB) is one of the most common obstetric problems, and preterm neonates are more likely to die than term infants. Furthermore, those who survive run a greater risk of disability than term infants [(2)].

Platelets and lymphocytes share regulatory mechanisms in the pathophysiology of thrombosis, inflammation, immunity, and

PRECIS: Maternal platelet to lymphocytes ratio at delivery can predict poor neonatal outcome in preterm births

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atherosclerosis. The effect of platelets on lymphocyte function may be via direct contact or by soluble mediators [3]. Platelets enhance adhesion and cell migration of lymphocytes, and affect other functional aspects of lymphocytes in a complex manner[4].

The platelet-to-lymphocyte ratio (PLR) was suggested by previous studies to be a strong predictor of inflammation [3,5]. It is a good indicator of platelet activation, lymphocyte function, and immune response[3] In obstetrics, the PLR was previously studied as a new inflammatory marker for the diagnosis of preterm premature rupture of membranes,[6] as a predictor for severity of preeclampsia,[7-9] and Kurtoglu et al.[10] reported that it may be useful in the discrimination of benign and malignant endometrial lesions, and early and advanced-stage endometrial cancer.

Klement et al. [11] conducted a population-based study on the PLR among pregnant women. They found a maximum PLR value during the second trimester, which showed a positive correlation with maternal age. However, no differences were found between the high-risk and normal population, excluding patients with a fibroid uterus or inflammatory bowel disease who presented significantly elevated PLRs through all trimesters.

This study was conducted to investigate the relationship between maternal PLR at delivery and preterm neonatal outcomes in a group of mothers selected from 2 seaside cities in 2 different countries, the first was the city of Aden located on the Arabian sea (Yemen), and the second was Alexandria city located on the Mediterranean sea (Egypt), aiming to find a benefit in using maternal PLR in predicting neonatal outcomes in PTB.

Materials and Methods

This is a retrospective study conducted on 439 PTBs collected from Al-Sadaka Teaching Hospital in Aden (Yemen) and Al-Zohour Hospital, Sedi Beshr, in Alexandria (Egypt) during 2017. In addition, the records of 200 term pregnant women who delivered at the same hospitals during the same duration were used as a control group. Data collected included maternal age, parity, gestational age at delivery and neonatal outcome variables (birth weight, APGAR score at 5 minutes, morbidity, and mortality). The platelet count and the absolute lymphocyte count were taken from the complete blood count report at delivery, and then the PLR was calculated.

Ethical consideration

This study was conducted retrospectively after obtaining consent from the hospitals' directors and archive who requested to code personal data to numbers, and accordingly, there was no physical or psychological harm for the patients and controls included in this study.

Statistical Analysis

Data were processed using the SPSS program version 24. Quantitative variables found with parametric distribution are presented as means and standard deviations with ranges. Student's t-test was used to investigate the presence of a significant difference between the PTBs and controls. Qualitative variables were compared using the chi-square test and Fisher's exact test, as appropriate.

A receiver operating characteristics (ROC) curve was drawn for the PLR to obtain the cutoff value with the highest sensitivity and specificity. Then Pearson rank-order correlation tests were conducted between the PLR, gestational age, and birth weight of the PTBs. All statistical tests were conducted with 95% confidence intervals and a p value of ≤0.05 was considered statistically significant.

Results

In this study, there was no significant difference between the PTBs and controls regarding maternal age and parity. Only gestational age was statistically significantly higher among the controls. The mean lymphocyte count was significantly higher among the controls, and the mean PLR was significantly higher among the women with PTBs (Table 1).

Neonatal outcomes among the studied PTBs revealed significant poor outcome regarding birth weight, APGAR score, morbidity and mortality, when compared to the control (Table 2).

The ROC curve for PLR among the studied PTBs, showed significant area under the curve (AUC=0.647, p=0.026) (Figure 1). With a cutoff value of 80, there was no significant difference in the mean maternal age, parity and gestational age between the women with PTB with PLR <80 or PLR ≥80. A significant difference was evident in the mean platelet count, lymphocyte count, and PLR in both groups (Table 3).

Table 1. Basic data obtained from medical records of preterm births and the control

Item	PTB (n=439) Mean ± SD (Min-Max)	Control (n=200) Mean ± SD (Min-Max)	p value
Age (years)	28.0±3.8 (18-39)	27.9±3.3 (19-37)	0.748
Parity	3.6±1.3 (0-8)	3.4±1.1 (0-7)	0.059
Gestational age (weeks)	30.5±2.6 (24-35)	39.2±1.5 (37-42)	**0.0001***
Platelet count ($x10^9$/L)	248.3±82.4 (53.0-490.0)	237.1±80.3 (150.0-480.0)	0.109
Lymphocyte count ($x10^9$/L)	2.160±0.85 (1.01-3.378)	2.514±0.68 (1.10-3.348)	**0.0001***
PLR	130.8±81.4 (41.8-406.6)	105.6±55.9 (34.8-286.5)	**0.0001***

*Statistically significant PTB: Preterm birth, PLR: Platelet-to-lymphocyte ratio, Min: Minimum, Max: Maximum, SD: Standard deviation

Table 2. Neonatal outcomes for the preterm births and controls

Outcome	PTB (n=439)		Control (n=200)		p value
	№	%	№	%	
Low birth weight (<1500 g)	93	21.2	11	5.5	**0.001***
APGAR score <7 (5th min)	178	40.5	28	14.0	**0.001***
Respiratory distress syndrome	166	37.8	4	2.0	**0.001***
Sepsis	69	15.7	5	2.5	**0.001***
Intraventricular hemorrhage	33	7.5	1	0.5	**0.001***
Perinatal death	123	28.0	6	3.0	**0.001***

*Statistically significant PTB: Preterm birth

Table 3. Demographic and laboratory data of pregnant women with preterm births in relation to the platelet-to-lymphocyte ratio with a cut-off value of 80

Item	PLR <80 (n=96) Mean ± SD (Min-Max)	PLR ≥80 (n=343) Mean ± SD (Min-Max)	p value
Age (years)	28.3±1.6 (18–39)	27.9±1.9 (18–38)	0.060
Parity	3.7±1.2 (0–8)	3.5±1.0 (0–8)	0.099
Gestational age (weeks)	33.2±2.5 (26–36)	32.7±4.1 (24–36)	0.256
Platelet count (x109/L)	193.4±33.9 (53.0–254.0)	263.7±85.4 (88.0–490.0)	0.001*
Lymphocyte count (x109/L)	2.895±0.44 (1.104–3.378)	1.954±0.821 (1.010–3.378)	0.001*
PLR	67.1±8.8 (41.83–79.71)	148.6±57.8 (80.0–406.64)	0.001*

*Statistically significant PTB: Preterm birth, PLR: Platelet-to-lymphocyte ratio, Min: Minimum, Max: Maximum, SD: Standard deviation

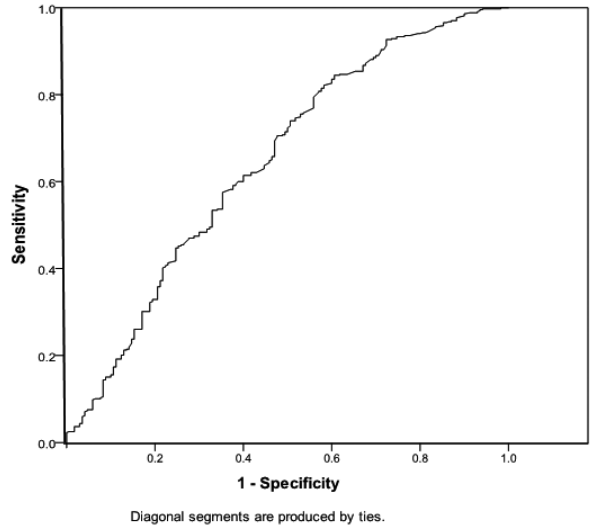
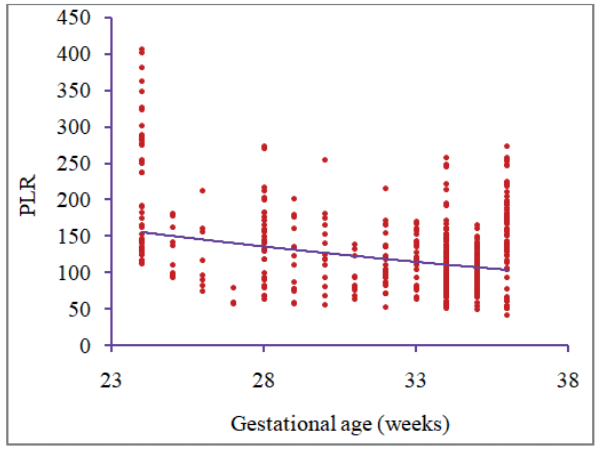


Figure 1. The receiver operating characteristic curve for the platelet-to-lymphocyte ratio



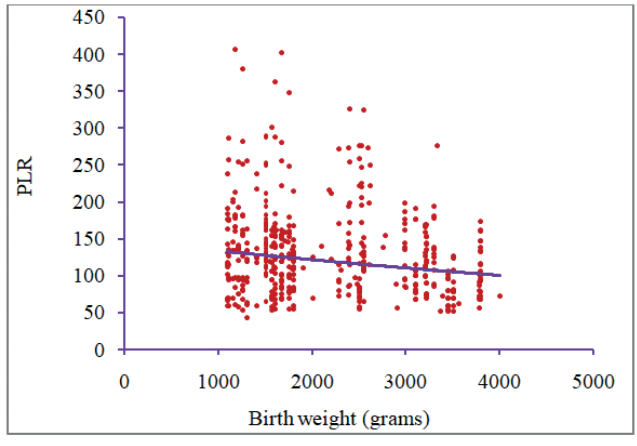


Figure 2. Negative correlation between the platelet-to-lymphocyte ratio and gestational age and birth weight

Table 4. The relationship between the platelet-to-lymphocyte ratio and neonatal outcomes for preterm births with a cut-off value of 80

Outcome	PLR <80 (n=96)		PLR ≥80 (n=343)		p value
	No	%	No	%	
Low birth weight (<1500 g)	14	14.6	79	23.0	0.073
APGAR score <7 (5th min)	30	31.3	148	43.1	**0.036***
Respiratory distress syndrome	26	27.1	140	40.8	**0.014***
Sepsis	9	9.4	60	17.5	0.053
Intraventricular hemorrhage	2	2.1	31	9.0	**0.022***
Perinatal death	19	19.8	104	30.3	**0.042***

*Statistically significant, PLR: Platelet-to-lymphocyte ratio

There was significant poor outcome for preterm neonates delivered to mothers with PLR ≥80. They showed a significantly higher percentage of neonates with low APGAR score, RDS, intraventricular hemorrhage, and perinatal death (Table 4).

The Pearson rank-order correlation test showed a significant negative correlation between PLR and birth weight (r=-0.189, p=0.001) as well as gestational age (r=-0.345, p=0.001) among the studied PTBs (Figure 2).

Discussion

Preterm neonates have poorly developed organ systems that put them at risk for many life-threatening conditions. They are at risk for hypothermia because they cannot produce and retain enough heat to maintain their body temperatures, respiratory distress syndrome from deficiency in surfactant production and lung development and bronchopulmonary dysplasia, cardiovascular abnormalities including patent ductus arteriosus and low blood pressure, intraventricular hemorrhage, ineffective glucose regulation, necrotizing enterocolitis, infection and retinopathy of prematurity.[12]

Different factors may play a role in poor obstetric outcomes such as PTB. These factors include high or low maternal age (>34 yrs and <17 yrs), smoking, alcohol or drug use during pregnancy, inadequate prenatal care, multiple pregnancies, nutritional status, co-morbidities such as hypertension, diabetes, and genitourinary tract infections, and certain biologic or genetic markers[13-15].

In the current study, a higher perinatal mortality rate was observed among PTBs. The earlier the gestational age, the greater the risk of morbidity and death. The relationship between mortality and immaturity (i.e. early gestational age at birth) is not linear but exponential. Though only 3-4% of births occur before 34 weeks, they account for the majority of neonatal deaths[16,17].

The PLR is a marker that can predict inflammation, thrombotic events, and malignancies. Previous reports showed a significant association between high PLRs and major adverse outcomes in renal diseases, and reduced survival in malignancies such as endometrial cancer[18-21].

The ROC curve for PLR in this study showed a significant AUC. This significant area may help in using the PLR among PTBs to predict neonatal outcome among preterm deliveries. When the cutoff value of 80 was used, preterm neonates delivered to mothers with PRL ≥80 showed significantly poor outcomes in APGAR score, RDS, intraventricular hemorrhage, and perinatal death.

In the current study, there was significant negative correlation between maternal PLR at delivery with birth weight and gestational age of PTBs. Similar findings were reported by Akgün et al.[22] in Turkey among 783 pregnant women; the authors concluded that PLR was negatively correlated with the week of birth and birth weight of the infant.

The ability to identify late-preterm infants who are prone to neonatal complications would be of great importance for counseling purposes. In the current study, maternal PLR at delivery was assessed in relation to neonatal outcomes among PTBs. Our findings suggest the use of maternal PLR at delivery as a prognostic marker for neonatal outcomes. The higher the PLR, the worse the neonatal outcomes in PTBs.

Conclusion and recommendation

Maternal PLR at delivery has a significant relationship with neonatal outcomes. It can predict preterm neonates with poor outcomes. Further studies are recommended for PLR in early pregnancy to identify pregnant women at risk of preterm delivery, who require special prenatal follow-up and preventive therapies to reduce the number of premature births.

Ethichs

Ethics Committee Approval: Retrospective study.
Informed Consent: It was obtained.
Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.W.J., Concept: D.W.J., M.A.F.R., Design: D.W.J., M.A.F.R., Data Collection or Processing: D.W.J., M.A.F.R., Analysis or Interpretation: M.A.F.R., Literature Search: D.W.J., M.A.F.R., Writing: D.W.J., M.A.F.R.

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

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Review / Derleme

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Basic clinical retroperitoneal anatomy for pelvic surgeons

Pelvik cerrahlar için temel klinik retroperitoneal anatomi

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Abstract

Basic anatomical knowledge should be improved during residency period with clinical practice. Especially pelvic surgeons; obstetricians, gynecologists, gynecological oncologists, urologists and general surgeons must have an advanced level practise of retroperitoneal anatomy to gain surgical skills. Retroperitoneal topographic anatomy, retroperitoneal vasculature, ureteric dissection and pelvic avascular spaces are the precise points during pelvic surgery.

Keywords: Surgery, anatomy, hypogastric, ureter, gynecology

Öz

Temel anatomik bilgi, tıpta uzmanlık için asistanlık döneminde klinik pratik ile beraber geliştirilmelidir. Özellikle pelvik cerrahlar; obstetrisyenler, jinekologlar, jinekolog onkologlar, ürologlar ve genel cerrahlar, cerrahi yetenekler kazanmak için retroperitoneal anatomiye ileri düzeyde hakim olmalıdır. Retroperitoneal topografik anatomi, retroperitoneal vaskülerizasyon, üreter disseksiyonu ve pelvik avasküler alanlar pelvik cerrahi için gerekli olan en hassas noktalardır.

Anahtar Kelimeler: Cerrahi, anatomi, hipogastrik, üreter, jinekoloji

Retroperitoneum

1. Topographic retroperitoneal anatomy

The posterior abdominal wall is the posterior boundary of the abdominal cavity, which is the continuous part of posterior thoracic wall from the level of diaphragm cranially and posterior pelvic wall caudally. The lumbar vertebra, pelvic girdle, posterior abdominal wall muscles [musculus (m) quadratus lumborum, m. psoas major, m. psoas minor, m. iliacus, and muscles of diaphragm] and their fascia are the members of this region.

The retroperitoneum is a part of the abdominal cavity; surrounded anteriorly by the parietal peritoneum and posteriorly by the transversalis fascia (Figure 1)[(1)]. It is a wide area from the pelvis to the diaphragm and contains numerous organs and structures; structures behind the peritoneum are called 'retroperitoneal' (Figure 2)[(2)]. The primary retroperitoneal organs are the adrenal glands, kidneys, ureter, the abdominal aorta, inferior vena cava and their branches. The secondary retroperitoneal organs, which were initially intraperitoneal and became retroperitoneal structures during embryologic development due to the regression of peritoneal tissue lying on the posterior wall of the abdominal cavity (the mesentery of these structures fuse with the posterior abdominal wall), are the ascending and descending colon, duodenum except the bulbus part (first half of duodenum segment 1) and pancreas.

Clinical tip: How to enter the retroperitoneal area?

When there is a distorted anatomy of peritoneal structures, to achieve a normal anatomy and resect all pathologic lesions, the surgeon needs to gain access to the retroperitoneum, which is mainly safe and that leads to a comprehensive dissection and visualization of the relevant anatomy.

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The peritoneal reflection between the round ligament [ligamentum (lig) teres uteri] (lateral) and infundibulopelvic ligament (medial) is an easy way to enter the retroperitoneum (Figure 3). Gentle traction on the lateral parietal peritoneal surface and cutting it either with scissors or energy devices is an easy and safe way of opening the retroperitoneum (Figure 4).

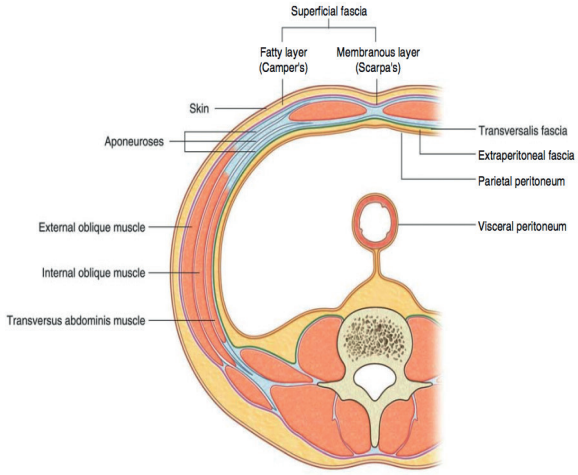

Figure 1. Transverse section of the anterior abdominal wall; the extraperitoneal fascia with fatty tissue under the parietal peritoneum lies on the posterior abdominal wall called the retroperitoneum (Gray's Anatomy for Students, 3rd Edition, Churchill Livingstone/Elsevier, 2015)[1]

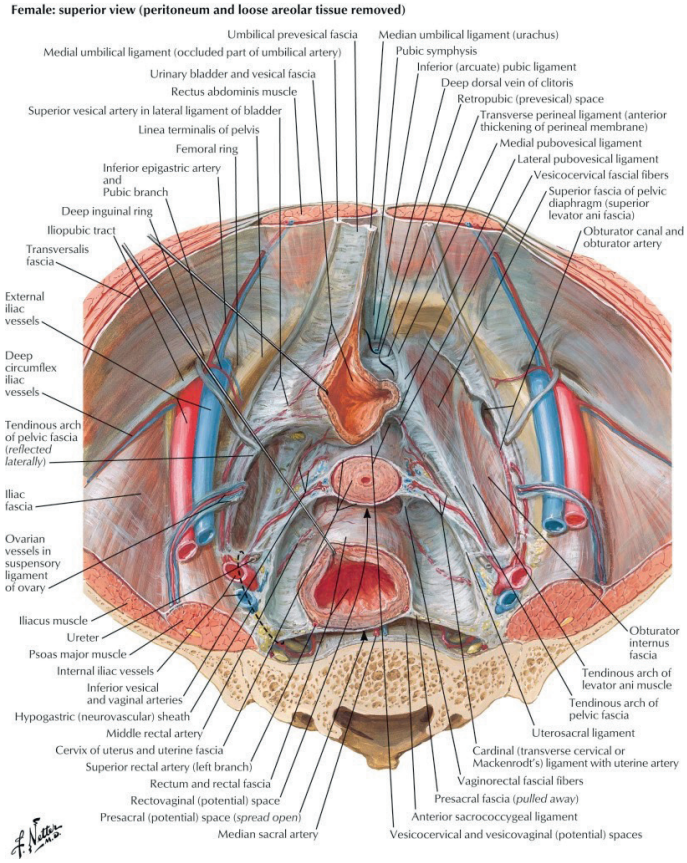

Figure 2. Pelvic viscera and retroperitoneum (Atlas of Human Anatomy, 6th Edition, Saunders/Elsevier, 2014)[2]

2. Pelvic retroperitoneal vasculature

A. Arteries

Abdominal aorta

The thoracic aorta is called the abdominal aorta because it enters the abdominal cavity through the diaphragm and it lies at the posterior abdominal wall, anterior to the vertebral column. The abdominal aorta is divided into the right and left common iliac arteries at the level of the L4-L5 vertebra, and the common iliac artery is divided into two parts as the external and internal iliac artery at the pelvic brim. The ovarian artery, median sacral artery, external iliac artery, internal iliac artery and its branches are important structures of pelvic retroperitoneal vasculature (Figure 5).

Ovarian artery: This is located on the anterolateral surface of the abdominal aorta, at the level of the L2 vertebra, generally

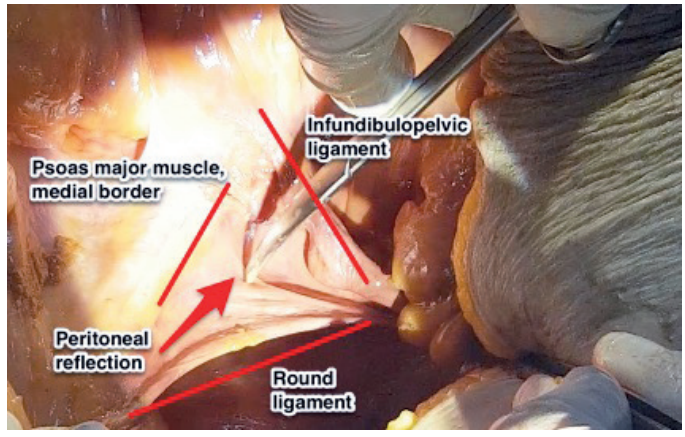

Figure 3. Demonstration to enter the retroperitoneum between the round ligament and infundibulopelvic ligament (lateral parietal peritoneum), right pelvic side wall (cadaveric dissection)

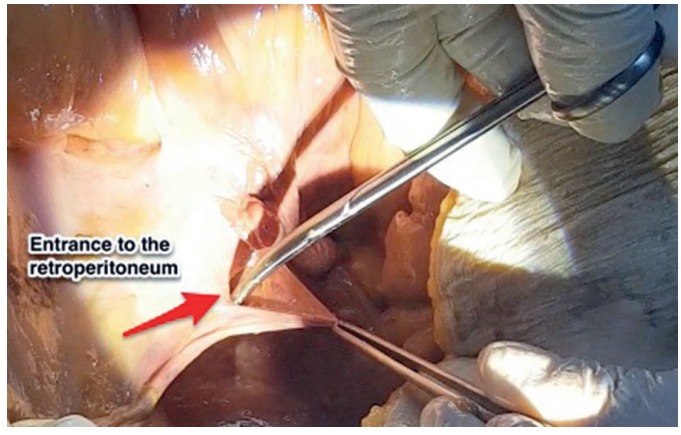

Figure 4. Demonstration of opening retroperitoneum, right pelvic side wall (cadaveric dissection)

2 cm below the level of the left renal vein. On the left side, it goes over the psoas major muscle and enters the pelvic cavity by crossing the common iliac artery. On the right side, first it crosses over the anterior surface of inferior vena cava then goes downward beside the ascending colon 1 cm above the right ureter and enters the pelvic cavity by crossing over the common iliac artery or sometimes the external iliac artery.

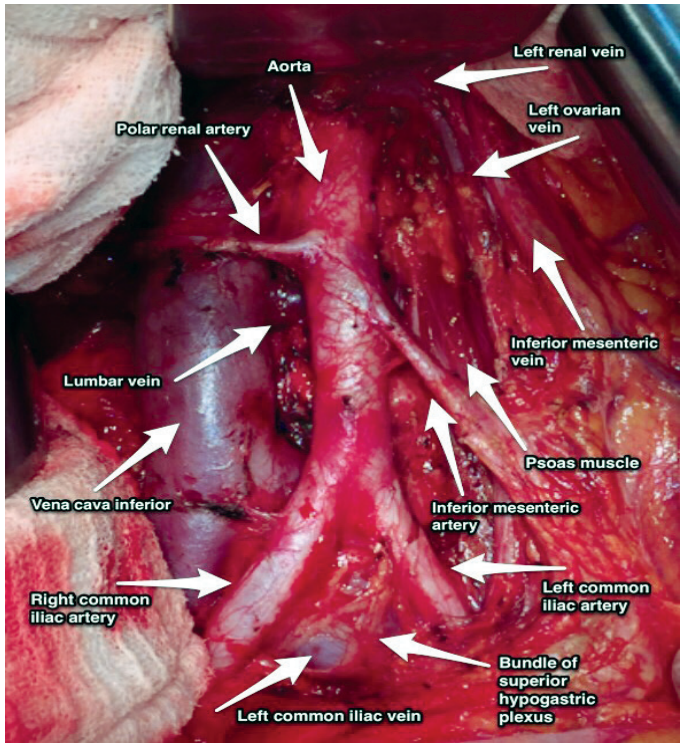

Figure 5. Paraaortic region, aorta and inferior vena cava after paraaortic lymphadenectomy (surgical archieve)

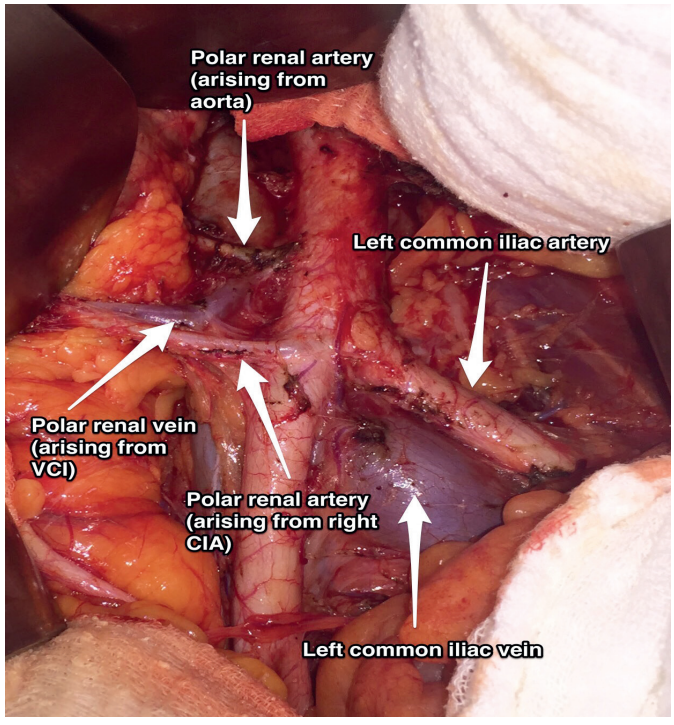

Figure 6. Polar renal artery arising from the right common iliac artery and also abdominal aorta (surgical archive)

VCI: Vena cava inferior, CIA: Common iliac artery

Median sacral artery: This is the continuation of the abdominal aorta on the anterior surface of the sacrum and coccyx. It is crossed by the left common iliac vein and care should be taken during hysteropexy and colpopexy operations.

Common iliac artery: The common iliac artery divides into the external and internal iliac artery. It is the point where polar renal arteries mostly arise (Figure 6); meticulous dissection is important during surgical procedures regarding this field[3].

External iliac artery: This goes along the medial border of the psoas muscle to the level of femoral ring, which is below the inguinal ligament. The genitofemoral nerve is found on the lateral border of the external iliac artery (lateral border of pelvic lymphadenectomy) (Figure 7). It is the principal artery of the lower limb. Its branches are the deep circumflex femoral artery and the inferior epigastric artery.

Internal iliac artery: This runs infero-medially after the pelvic brim and is the major vascular supply of the pelvic cavity. It has two trunks; posterior and anterior[4]. The branches of the posterior trunk are the superior gluteal artery, lateral sacral artery, and iliolumbar artery. The branches of the anterior trunk are the umbilical, uterine, superior and inferior vesical, vaginal, obturator, middle rectal, internal pudendal and inferior gluteal artery (Figure 7).

Clinical tip: Internal iliac artery and peripartum bleeding

During intractable pelvic hemorrhage or peripartum bleeding, ligation of the anterior trunk of the internal iliac artery bilaterally will decrease the amount of bleeding dramatically because the internal iliac artery is the major vascular supply of the pelvic cavity.

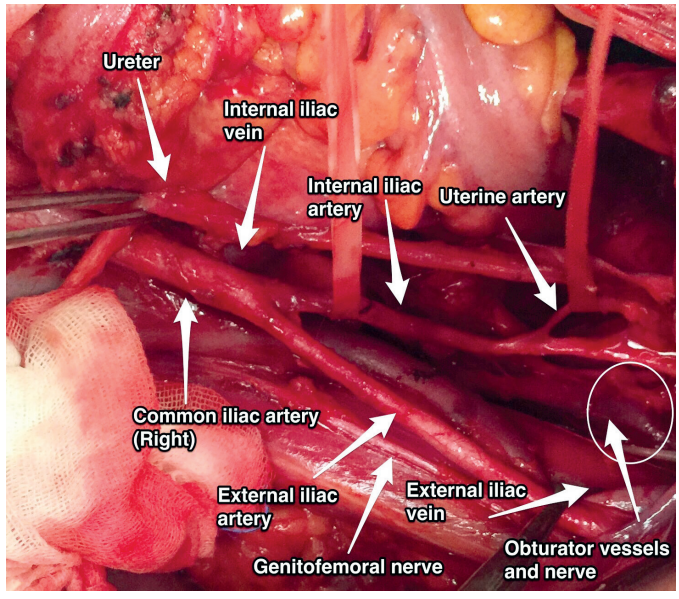

Figure 7. Uterine artery, right pelvic side wall (surgical archive)

Umbilical artery: This is the end artery of the internal iliac artery (anterior trunk). It goes longitudinally to the abdominal wall and becomes the medial umbilical ligament. When traction is applied to the umbilical artery during laparoscopic procedures, it will indicate the origin of the uterine artery.
Uterine artery: The uterine artery arises from the anterior trunk and goes medially through the broad ligament (lig. latum uteri) [within the cardinal ligament (lig. transversum cervicis)] towards the isthmic portion of the uterus to supply the uterus and cervix (Figure 7). It crosses the ureter close to the uterus.

B. Veins

Inferior vena cava

The inferior vena cava (IVC) begins just inferior to the L5 vertebra, where the abdominal aorta has a bifurcation of common iliac arteries. Under the level of the umbilicus, it is slightly at the posterior plane of the abdominal aorta. It ascends over the right psoas major muscle, right to the aorta, and above the level of umbilicus it gets closer to the anterior line of the abdominal aorta (Figure 5).

Clinical tip: Renal vein and ovarian vein

The left renal vein crosses over the abdominal aorta below the origin of the superior mesenteric artery and drains into the vena cava inferior. It receives blood from the left ovarian and adrenal veins and ascending lumbar vein. On the right side, the ovarian vein enters directly into the IVC.
External iliac vein: This is the continuation of the femoral vein above the inguinal ligament and runs on the posterior side of the external iliac artery.
Pubic vein: This is a vascular connection between the external iliac/inferior epigastric and obturator vein, and hemorrhage of this vein is called corona mortis. It is on the posterior part of pubic bone over the obturator fossa (Figure 8). This area is dissected during pelvic lymphadenectomy in gynecologic oncology practice, and the surgeon should be careful to prevent hemorrhage from this venous connection[5].
Internal iliac vein: Corresponding branches of the internal iliac artery generally run with their veins. There are numerous anomalous and collateral veins that drain into the internal iliac vein.
Common iliac vein: This starts from the conjunction point of the internal and external iliac veins and forms the inferior vena cava with its counterpart.

Clinical tip: Promontorium

It is at the upper part of pelvic cavity on the medial side of sigmoid colon. Transparietal fixation of the perisigmoid and perirectal fatty tissue or fixation of the sigmoid colon by appendix epiploicas after mobilization may provide adequate exposure of this field. The median sacral artery and left common iliac vein are just superior to the promontorium and the internal iliac artery with the ureter are in close connection at the lateral part.

Clinical tip: Left common iliac vein

It is a potential danger point during dissection of the field of the promontorium, which lies on the medial part of the left common iliac artery (Figure 9). During laparoscopic surgery, obesity and bad trocar angles will increase the likelihood of an injury to the left common iliac vein.

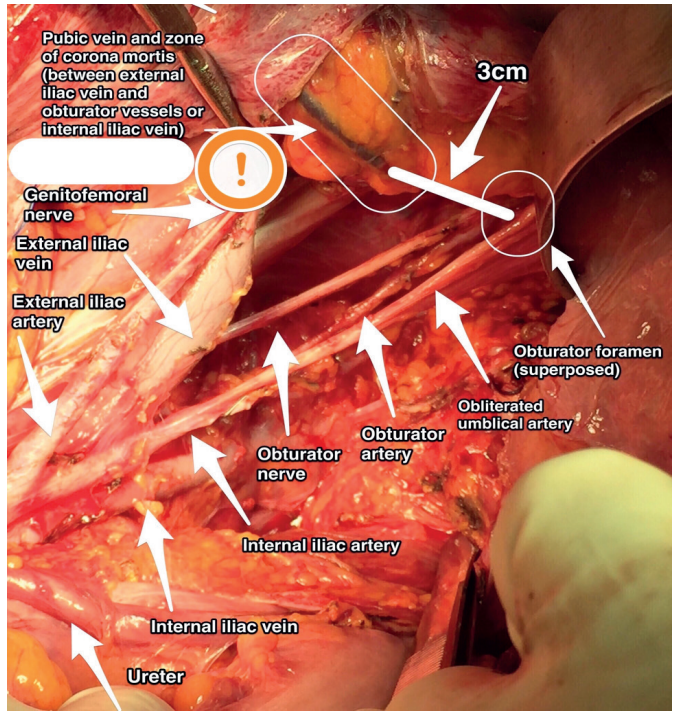

Figure 8. Pubic vein, left pelvic side wall (surgical archive)

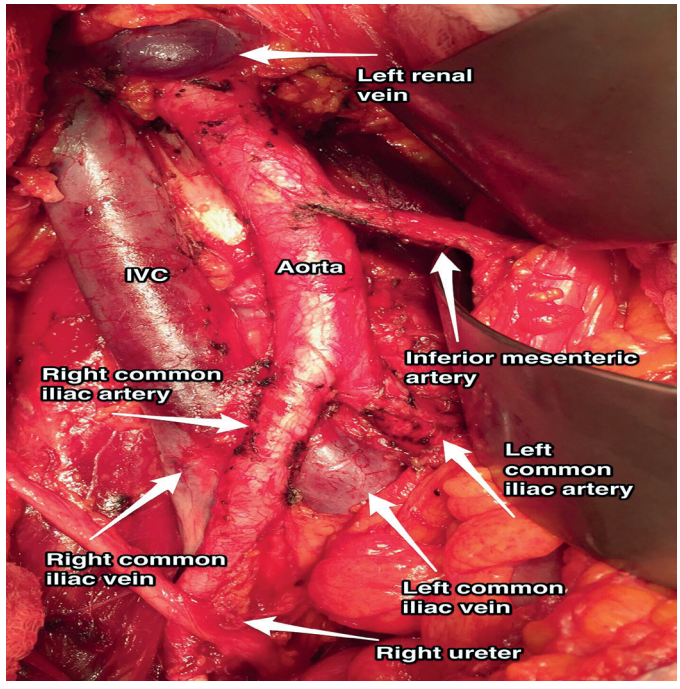

Figure 9. Left and right common iliac veins and arteries (surgical archive)

IVC: Inferior vena cava

3. Ureter

The ureter is a muscular structure, functioning in the transport of urine from the kidney to the bladder. It is about 23-30 cm in length. The renal pelvis narrows as it passes through the hilum of the kidney and forms the ureter, which continues inferiorly. After crossing the bifurcation of the common iliac arteries or the origin of the external iliac artery over the pelvic brim, it goes on the medial side of the psoas major muscle and runs along the posterior leaf of the broad ligament before entering the urinary bladder.

The distal ureter is crossed by the uterine artery antero-superiorly. The end part of the distal ureter enters the bladder obliquely to the smooth muscle wall of the bladder, providing a sphincter-like action.

The narrowest points of the ureter:

-The ureteropelvic junction
-Pelvic brim, where the ureters cross the common iliac vessels
-The ureterovesical junction, where the ureters enter the smooth muscle wall of the bladder

Anatomically, the ureter is divided into abdominal, pelvic, and intravesical parts. The abdominal part is on the medial border of the psoas muscle fascia over the genitofemoral nerve. The right ureter starts from the level where the posterior of the second part of duodenum is found and descends within the peritoneum of the ascending colon close to the right colic and ileocolic artery, lateral to the root of the small bowel mesentery and inferior vena cava under the ovarian vessels. Afterwards, it passes posterior to the terminal ileum and cecum. The left ureter descends on the lateral part of the abdominal aorta over the psoas muscle fascia and crossed anteriorly by the left colic artery and ovarian vessels. During this course of the left ureter, it lies parallel to the inferior mesenteric vein (Figure 10) and passes along the posterior of the sigmoid colon. The ureters cross the bifurcation of the common iliac artery over the pelvic brim.

When the ureter enters the true pelvis, it runs inferior to the ovarian vessels, and goes through that path to the bladder on the posterior leaf of the broad ligament. It goes antero-medially while crossing the uterine artery (water under the bridge) afterwards, it enters the ureteric tunnel (web tunnel) within the cardinal ligament. The ureter passes lateral to the antero-lateral vaginal fornix within the bladder pillar and enters the trigone of the bladder. The orifices of the ureters are seen on the postero-lateral part of the trigone. The ureters take a 1.5-2 cm course in the bladder wall.

The ureter does not have a primary arterial vessel for blood supply, it receives arterial branches from the renal, ovarian, common iliac, internal iliac, uterine, superior gluteal, vaginal, middle rectal, inferior and superior vesical arteries through its pathway from the renal pelvis to the bladder (Figure 11)[6]. These blood vessels anastomose with each other and shape a continuous longitudinal blood supply.

The ureters are very rich in innervation and they shape the ureteric plexus. The primary sensation of the ureter

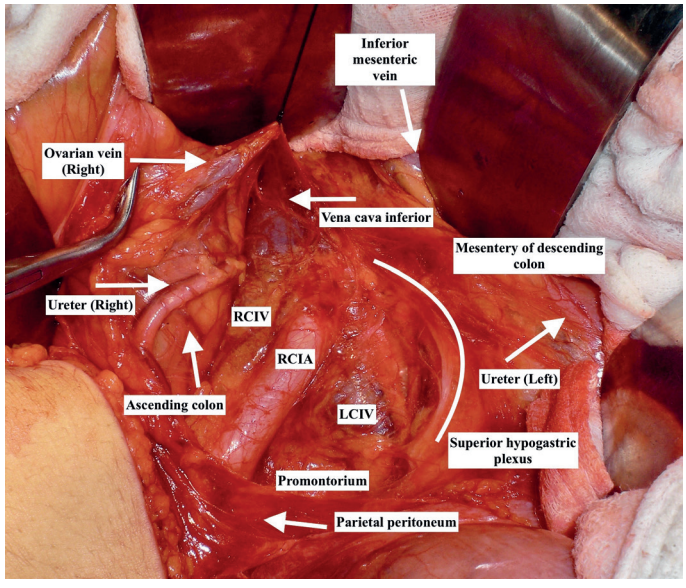

Figure 10. Right ureter below the right ovarian vein medial to the ascending colon and lateral to inferior vena cava, and left ureter underneath the mesentery of descending colon, medial/parallel to the inferior mesenteric vein and lateral to aorta/superior hypogastric plexus (surgical archive)

RCIV: Right common iliac vein, RCIA: Right common iliac artery, LCIV: Left common iliac vein

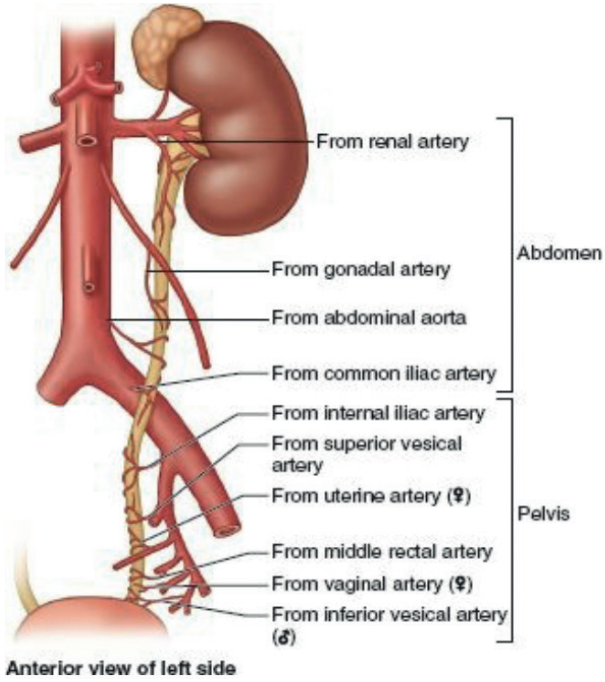

Figure 11. Vascularization of ureter from the kidney to the bladder (left side), while dissecting the ureter traction should be applied towards the side of blood vessels (Moore Clinically Oriented Anatomy, 7th Edition, Wolters Kluwer/Lippincott Williams & Wilkins, 2013)[6]

(visceral afferent fibers) is provided by nerves from T12-L2 (sympathetic system). Visceral efferent fibers come from both sympathetic and parasympathetic bundles.

Clinical tip: Vascularization of ureter

Injury to the longitudinal blood vessels of the ureter may cause ischemia or necrosis on the adventitia of ureter. If the adventitia of the ureter is not stripped or the fatty tissue over it (mesoureter in clinical term) has not been sacrificed, the surgical mobilisation of the ureter could easily be performed while avoiding injuries. Internal iliac artery is the most important vascular supply of ureter in the pelvis (Figure 12).

Clinical tip: Ureter injuries

During infundibulopelvic (IP) ligament ligation, where the ureter passes inferior to it, especially when the anatomy is distorted because of tumors, masses or severe adhesions, the IP ligament should be isolated and the ureter must be dissected to avoid injuries.

The ureter, where it crosses under the uterine artery above the vaginal artery, near the isthmic part of the uterus, is a site of injury during uterine artery ligation while performing hysterectomy. The ureter stands very close to the cervix, and to avoid injuries, the uterus must be pulled towards the other side cranially to maximize the distance between the ureter and the cervix.

After crossing the uterine artery, the ureter passes very close to the anterolateral part of vagina and during cardinal-uterosacral ligament ligation, the ureter will be injured (Figure 13).

4. Avascular spaces in the pelvis

Pelvic connective tissue divides the subperitoneal pelvic area into different spaces. These spaces are filled by fatty or loose areolar connective tissues, which are generally avascular. These potential spaces have a role in the functioning of urinary, reproductive, and gastrointestinal systems. They have a crucial role in the management of pelvic operations because knowing them exactly allows restoration of normal anatomy and avoids injury of pelvic viscera and structures. These pelvic spaces are as follows (Figure 14)[7]:

- Retropubic (Retzius) space
- Paravesical space
- Presacral (Retrorectal) space
- Pararectal space
- Vesicovaginal (Vesicouterine) space
- Rectovaginal space

Retropubic (Prevesical/Retzius) space

This is the potential extraperitoneal space between the bladder and the pubic bone that generally contains fat. Its boundaries are (Figure 15):

- Anteriorly: Pubic symphysis,
- Posteriorly: Bladder,
- Superiorly: Parietal peritoneum (anterior abdominal wall),
- Laterally: Arcus tendinous fascia pelvis and ischial spines.

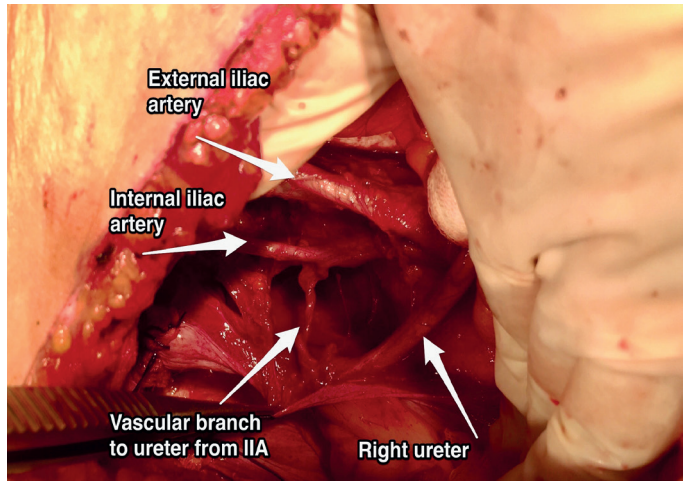

Figure 12. Vascular branch to ureter from internal iliac artery, right pelvic side wall, in the pelvis the most important vascular supply of the ureter is the branch from the internal iliac artery (surgical archive)

IIA: Internal iliac artery

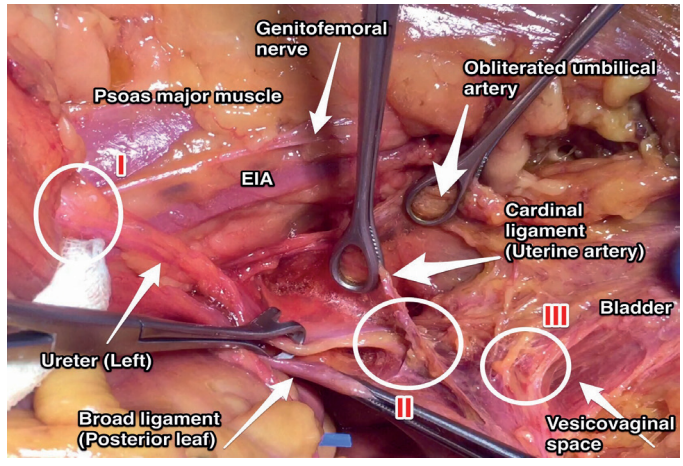

Figure 13. Sites of ureter injury, left pelvic side wall: Zone I, during infundibulopelvic ligament ligation just below the level of pelvic inlet; zone II, during uterine artery ligation (ureter crosses the cardinal ligament-uterine artery complex); zone III, during vaginal excision (ureter is anterolateral to the anterior vagina before entering the bladder-trigone) (cadaveric dissection)

EIA: External iliac artery

Grasping the median umbilical ligament (Urachus) with downward traction and cutting it will open the space of Retzius. The dorsal clitoral neurovascular bundle is found at the midline, and the obturator nerve bundle is located on the lateral plane. An accessory obturator artery from the external iliac artery that runs along the posterior part of pubic bone or a pubic vein from the external iliac vein or an arterial branch from the inferior epigastric artery will be detected at the lateral border of that field during its path to obturator

foramen. Moreover, lateral to the bladder neck and urethra, nerves innervating the bladder and urethra and a venous plexus (Santorini plexus), (which could be injured during suture placement for Burch retropubic colposuspension) are found.

Clinical tip: Burch colposuspension

This is a retropubic colposuspension operation for stress urinary incontinence in which the sutures starting from the paravaginal tissue are anchored to the ileopectineal ligament (Cooper's ligament), the superior border of the ischiopubic rami to maintain the tension on bladder neck and urethra.

Paravesical (and paravaginal) space

This is located within the lateral part of the Retzius space anterior to the cardinal ligament, bilaterally. Its boundaries are (Figure 16):

- Superiorly: Lateral umbilical folds (peritoneal thickening of inferior epigastric vessels),
- Inferiorly: Pubocervical fascia where it enters into the tendinous structure of levator ani muscle, iliococcygeus muscle,
- Anteriorly: Superior pubic ramus, arcuate line of the os ilium,
- Posteriorly: Endopelvic fascial sheath that covers the internal iliac artery and vein, cardinal ligament which separates it from the anterior part of pararectal space and uterine artery,
- Medially: Bladder pillars,
- Laterally: Pelvic side wall, obturator internus and levator ani muscle.

Lateral to the median umbilical ligament, after detecting the lateral border of bladder, the medial umbilical ligament (obliterated umbilical artery) can be identified and it divides the paravesical space into two parts (medial and lateral).

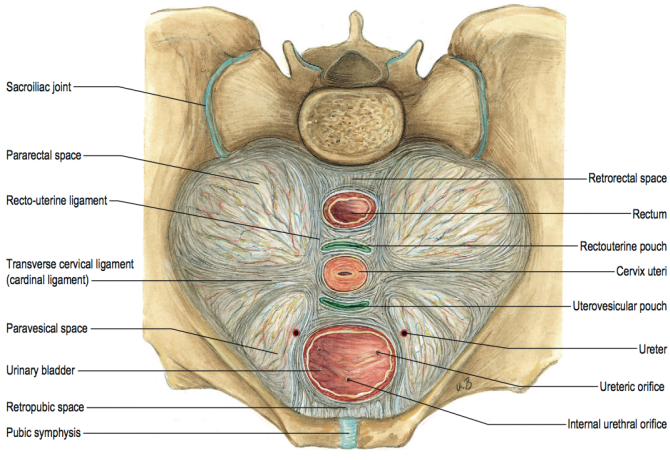

Figure 14. Avascular spaces and supporting ligaments in the pelvis (Sobotta Atlas of Human Anatomy, 15th Edition, Elsevier, Urban&Fischer. Copyright 2013/Gray's Anatomy, The Anatomical Basis of Clinical Practice, 41th edition, Elsevier, 2016)[7]

The lateral part is the obturator space (under the external iliac vessels) and the medial part is the ventral parametrium. The obturator space contains (Figure 8) the obturator nerve, obturator artery and vein, and fatty and lymphatic tissue. During pelvic lymphadenectomy to dissect the obturator lymph nodes, the surgeon needs to open the paravesical space first then dissect the lateral part on the pelvic side wall. Over the obturator fossa, there are numerous anomalous and collateral vessels, which need tiny and careful dissection to prevent hemorrhage due to injury[8]. Paravesical space contains obliterated umbilical artery and it is in close relation with obturator neurovascular bundle and external iliac vessels with the lymphatic and fatty tissue[9].

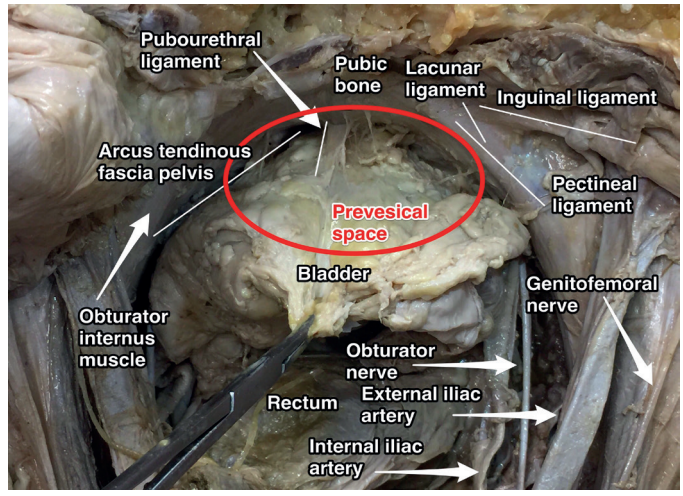

Figure 15. Prevesical space and contents (cadaveric dissection)

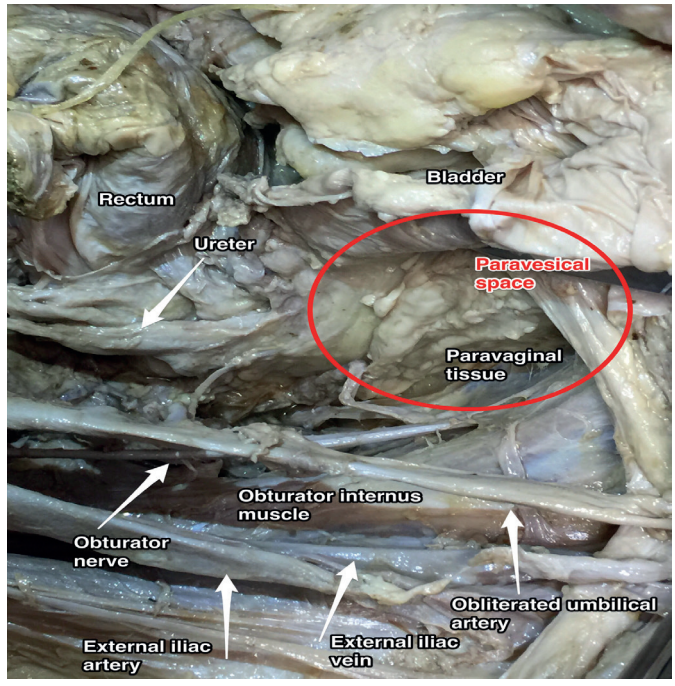

Figure 16. Paravesical space, right pelvic side wall (cadaveric dissection)

Clinical tip: Paravesical space

The paravesical space is generally accessed during Burch colposuspension, paravaginal defect repair, pelvic lymphadenectomy and some endometriosis operations after opening the retroperitoneal space entirely.

Radical hysterectomy is another surgical procedure that needs adequate exposure of the paravesical space during the operation. After opening the retroperitoneal space by transecting the round ligament and cutting the anterior leaf of broad ligament infero-medially, the place lateral to the median umbilical ligament (medial to round ligament), adjacent to the bladder, is the paravesical space and it develops inferiorly to the level of levator ani muscle.

Presacral (retrorectal) space

The retrorectal space is between the rectum and the sacral-coccygeal part of spine. The presacral space is a retroperitoneal area, which is between the presacral fascia of the sacrum (Waldeyer's fascia) and parietal peritoneum of the posterior abdominal wall. Its boundaries are (Figure 17):

- Superiorly: Peritoneal (parietal) reflections,
- Anteriorly: Distal portion of the sigmoid mesentery, posterior rectal fascia, rectum,
- Posteriorly: Anterior longitudinal ligament, sacral promontorium and anterior part of the sacrum,
- Inferiorly: Levator ani and coccygeus muscle,
- Laterally: Ureter, internal iliac vessels and hypogastric nerves.

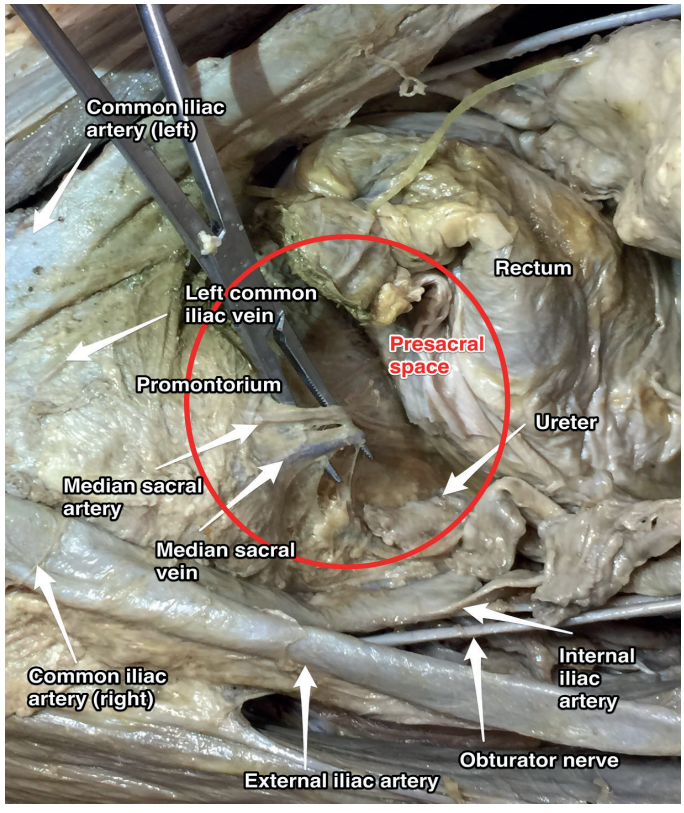

Figure 17. Presacral space (cadaveric dissection)

The presacral space starts from the parietal peritoneal reflection at the rectosigmoid junction to the pelvic bottom, which contains fatty tissue, lymph nodes, nerve plexuses and blood vessels, median sacral vessels (the artery is from the aorta) and superior rectal vessels (the artery is from the inferior mesenteric artery).

Clinical tip: Presacral space

There may be some anatomic variations in this field; presacral anastomoses between the lateral and middle sacral veins need careful dissection during surgery. Moreover, it is very close to the hypogastric nerves and sympathetic trunk. Below the level of the aortic bifurcation, the left common iliac vein crosses the sacral promontorium from right to left. The median sacral artery is detected at the midline or very close to the midline over the sacrum, so care must be taken during sacrocolpopexy procedure and paracoccygeal procedures. The superior hypogastric plexus may also be seen at the superior part of the presacral space over the sacral promontorium (Figure 18).

Primary lesions of this area are rare; however, lesions from adjacent structures may be seen in this field. After rectal or rectosigmoid resections, this field could be a place for accumulation of fluid leakages.

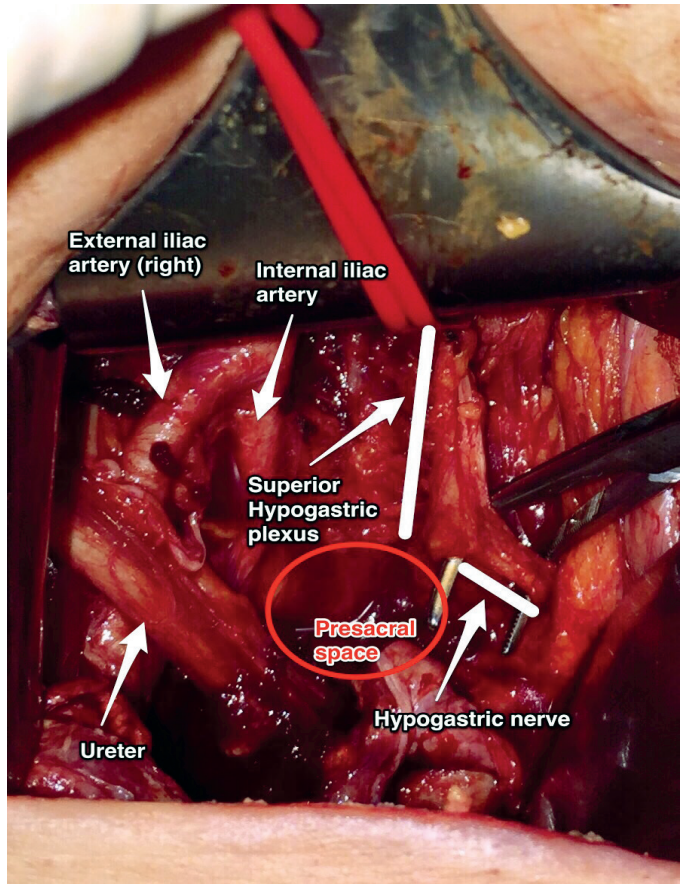

Figure 18. Presacral space and superior hypogastric plexus (surgical archive)

Clinical tip: Presacral hemorrhage

A serious bleeding may happen because of injuries of the middle sacral artery or vein particularly due to anastomoses. If the vessel structure is retracted into the sacral foramina, it will be harder to control the hemorrhage. A thumb tack could be applied if needed.

Pararectal space

The pararectal space is located lateral to the rectum and retrorectal space, and it is at the posterior part of the cardinal ligament. Its boundaries are (Figure 19):

- Anteriorly: Cardinal ligament,
- Medially: Rectal pillars, uterosacral ligament, ureter,
- Laterally: Internal iliac artery,
- Posteriorly: Sacrum,
- Caudally: Puborectalis muscle.

It contains fatty and connective tissue, and the ureter passes along the pararectal space at the medial part. After a tiny dissection of the ureter within the pararectal space, the ureter will divide it into two parts; medial is Okabayashi's space and lateral is Latzko's space (Figure 20). It is separated from the paravesical space by the cardinal ligament/uterine artery and from the presacral space by the rectal septa.

Okabayashi's space

The medial pararectal space is called Okabayashi's space and it is between the ureter and the rectouterine ligament, which is developed after opening the posterior leaf of the broad ligament (Figure 20).

Latzko's space

The lateral pararectal space is called Latzko's space and it is between the ureter and pelvic side wall, which is developed after dissection of internal iliac artery (Figure 20). Middle rectal artery could be seen at the lateral rectal wall by the way the pelvic splanchnic nerves and the fibers of the inferior hypogastric plexus, which lies under the middle rectal artery, could be preserved.

Clinical tip: Pararectal space

When the pouch of Douglas (rectovaginal space) is obliterated by a tumor, severe adhesions or endometriosis, the surgeon should primarily open the retroperitoneal space, find the ureter, and after ureterolysis the pararectal space should be developed to dissect the rectum from the vagina and open the rectovaginal space.

During radical hysterectomy, the pararectal space should be developed to excise the cardinal ligament entirely. After dissection of the posterior leaf of the broad ligament postero-medially, the pararectal space is developed between the ureter and internal iliac artery anterior to the sacrum.

Vesicovaginal (Vesicouterine) space

The vesicovaginal, vesicocervical, and vesicouterine spaces are all at the same longitudinal axis and this area is also known as the anterior cul-de-sac. The boundaries of the vesicocervical space are (Figure 21):

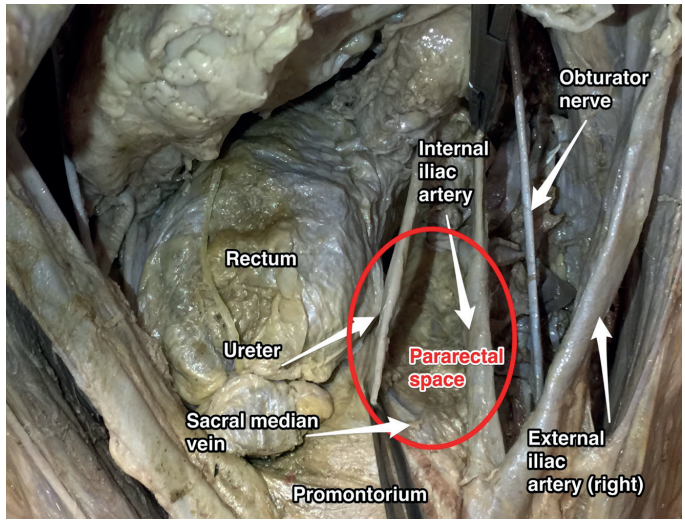

Figure 19. Pararectal space, right pelvic side wall (cadaveric dissection)

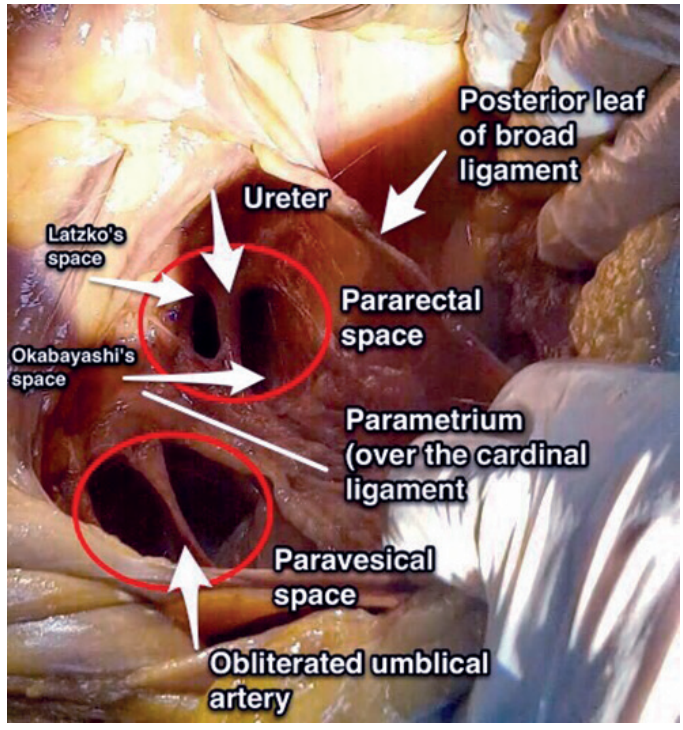

Figure 20. Right pelvic side wall; the paravesical space, anterior to the cardinal ligament is divided into two parts by the obliterated umbilical artery and the pararectal space, posterior to the cardinal ligament is divided into two parts by the ureter, the lateral part is called Latzko's space and the medial part is called Okabayashi's space (cadaveric dissection)

- Anteriorly: Posterior part of the bladder,
- Posteriorly: Cervix,
- Laterally: Bladder pillars (superior portion, that is divided by the ureter), pubocervical ligament (vesicouterine ligament in clinical term)[10],
- Superiorly: Anterior peritoneal fold, vesicouterine peritoneal fold.

The boundaries of the vesicovaginal space:

- Anteriorly: Trigone of bladder,
- Posteriorly: Vagina,
- Laterally: Bladder pillars, pubocervical ligament,
- Inferiorly: Urogenital diaphragm.

After cutting the vesicouterine pouch (between the dome of the bladder and the anterior part of the uterus) and with posterior traction of uterus towards the promontorium, this field can be opened easily. The lateral bladder pillars contain blood vessels, vesical veins (inferior, superior), cervical terminal branches from the uterine artery, and connective tissue from the cardinal ligament.

Clinical tip: Vesicovaginal space

During radical hysterectomy before excising the anterior parametrium, the bladder should be dissected to the level of the trigone, afterwards the ureter should be dissected from the parametrium. Moreover, vesicovaginal space dissection should be performed medially at the midline within the loose areolar tissue because lateral extensions during dissection could cause bleeding from the bladder pillars (vesical veins).

Rectovaginal space

The rectovaginal space is from the recto-uterine peritoneal fold (pouch of Douglas) to the level of the perineal body. Access to this area can be maintained by cutting the recto-uterine peritoneal structure between the insertions of the uterosacral ligament, which lie bilaterally. Its boundaries are (Figure 22):

- Anteriorly: Posterior wall of the vagina,
- Posteriorly: Anterior wall of the rectum,
- Laterally: Uterosacral ligament, rectal pillars.

Clinical tip: Rectovaginal space

The recto-uterine, recto-vaginal pouch will be enclosed by severe adhesions due to endometriosis, tumor or abscess. Dissection of the vagina from the rectum and uterosacral ligaments after developing the pararectal space can maintain an extra field for surgery. The loose areolar tissue between the rectum and vagina can be bluntly dissected easily; however, the fatty tissue in this area belongs to the rectum. The rectal pillars are fibro-connective tissues, which are vascularized by the middle rectal arteries from the internal iliac artery over the cardinal ligament[11].

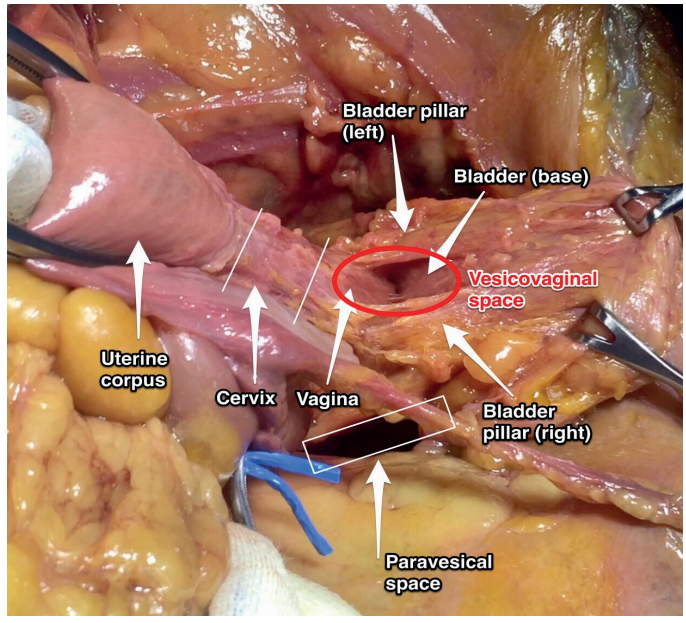

Figure 21. Vesicovaginal space (cadaveric dissection)

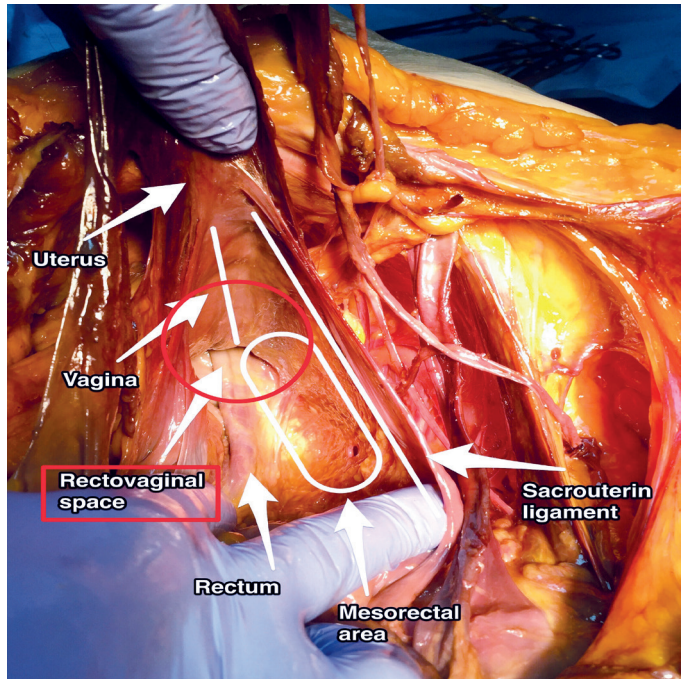

Figure 22. Rectovaginal space (cadaveric dissection)

Clinical tip: Cervical fibroids

Both the vesicouterine and rectouterine pouch (anterior and posterior cul-de-sac) should be cut, the bladder should be dissected downward to the level of anterior vagina, and the ureter must be identified bilaterally. In particular, lateral to the rectovaginal space, the ureter is in close proximity to the uterosacral ligaments (at the lateral part of uterosacral ligaments) and meticulous dissection should be applied with regard to the vascular connections and depth of a cervical mass[12].

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Case Report / Olgu Sunumu

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Chorangiosis placenta with 5-vessel umbilical cord with omphalomesenteric duct remnant: An unusual association

Omfalomezenterik kanal kalıntısı olan 5-damarlı umbilikal kordon ile koranjiyozis plasenta: Sıradışı bir ilişki

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Abstract

Placenta is an organ that is responsible for nourishing and protecting the fetus during pregnancy. Histologic examination of the placenta can yield significant information about pre-uterine and uterine conditions affecting fetal growth. Chorangiosis is defined as the presence of ≥10 terminal villi, each containing ≥10 capillaries per terminal villus in ≥10 low power (×10) fields in at least 3 or more random, non-infarcted cotyledons of the placenta. Chorangiosis is an adaptive response to in-utero hypoxia and its presence signifies better pregnancy outcomes. Abnormalities that lead to multiple cord vessels are rare with the majority of reported cases highlighting four vessels due to a persistent right umbilical vein. We report here a case of chorangiosis of placenta associated with a rare 5-vessel umbilical cord and omphalomesenteric duct remnant. To the best of our knowledge, this is the first case report to document such an association.

Keywords: Placenta, umbilical cord, chorangiosis

Öz

Plasenta, gebelik sırasında fetüsün beslenmesinden ve korumasından sorumlu bir organdır. Plasentanın histolojik incelemesi, fetal büyümesini etkileyen ön uterin ve uterinin durumları hakkında önemli bilgiler verebilmektedir. Koranjiyozis, büyütmede düşük güç (x10), plasentanın en az 3 veya daha fazla rastgele, enfarkte olmayan kotiledonundaki ≥10 alanda, her biri ≥10 kapiller içeren ≥10 terminal villus bulunmasıyla tanımlanır. Koranjiyozis iç uterin hipoksisine uyarlanabilir bir yanıttır ve varlığı daha iyi gebelik sonuçları anlamına gelir. Çoklu kordon damarlarına yol açan anormallikler nadirdir, bildirilen vakalarda çoğunlukla persistan sağ umbilikal vene bağlı dört damar vurgulanmaktadır. Bu çalışmada, nadir görülen 5 damarlı umbilikal kordon ve omfalomezenterik kanal kalıntıları ile ilişkili bir koranjiyozis plasenta vakası sunulmuştur. Bildiğimiz kadarıyla bu çalışma, böyle bir ilişkiyi belgeleyen ilk vaka raporudur.

Anahtar Kelimeler: Plasenta, umbilikal kordon, koranjiyozis

Introduction

The placenta is an organ that is responsible for nourishing and protecting the fetus during pregnancy. Histologic examination of placenta can yield significant information about pre-uterine and uterine conditions affecting fetal growth. One of the histo-morphologic features to be evaluated is the vascularity of chorionic villi. The number of vascular channels present in terminal villi ranges from 2 to 6 and if the number increases beyond this then it is termed as 'villous hypervascularity[1].' The term 'chorangiosis' was introduced by Altshuler in 1984 and is defined as the presence of ≥10 terminal villi, each containing ≥10 capillaries per terminal villus in ≥10 low power (10×) fields in at least 3 or more random, non-infarcted cotyledons of the placenta[2].

PRECIS: We report here a case of chorangiosis of placenta associated with the rare 5-vessel umbilical cord and omphalomesenteric duct remnant.

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Chorangiosis is known to occur as an adaptive response to chronic low-grade placental hypoxia[1]. It has been found to be associated with various maternal, fetal and placental disorders[1]. Rarely, its association has also been demonstrated with umbilical cord anomalies such as true and false knots, long cord, umbilical vein dilatation or thrombosis, nuchal cord, and single umbilical artery[3]. Herein, we report a case of chorangiosis of placenta associated with the rare 5-vessel umbilical cord.

Case Report

A 27-year-old female, para-3-live-1, with gestational hypertension and oligohydramnios presented to the gynecologic emergency at 34 weeks' gestation in labor. Emergency lower segment cesarean section was perfomed in view of fetal distress. The child was born with a birth weight of 1.6 kg and was stable. There were no congenital anomalies in the child. The placenta was sent for histopathologic examination. On gross examination, the placenta was complete and measured 12×11×3 cm with the attached umbilical cord measuring 18 cm in length. The umbilical cord contained 5 blood vessels (Figure 1a). On microscopy, sections from the placenta revealed ≥10 capillaries each in ≥10 terminal villi in ≥10 non-infarcted areas examined in ≥3 low power (10×) fields of placenta (Figures 1b, c). Immunohistochemically, the capillary endothelial cells showed uniform positivity with CD34, demonstrating more capillaries than were easily discernible using hematoxylin-eosin staining (Figure 2a), and staining for smooth muscle actin (SMA) was negative (Figure 2b). There was no evidence of increased cellularity or fibrosis in the stroma. Sections from hemorrhagic areas showed ischemic necrosis (Figure 1d). Sections from the umbilical cord showed 5 blood vessels; 4 arteries and 1 vein (Figure 2c) and an omphalomesenteric duct remnant (Figure 2d). Placental membranes were histopathologically unremarkable. A diagnosis of chorangiosis placenta with 5 blood vessels and omphalomesenteric duct remnant in the umbilical cord was given.

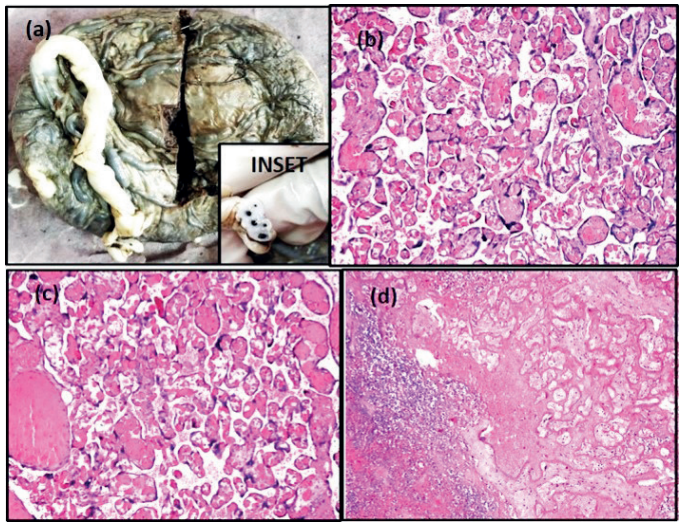

Figure 1. (a) Gross appearance of the placenta with attached umbilical cord. Inset showing umbilical cord with 5 blood vessels, (b, c) (100x) H/E-stained sections from the placenta showing ≥10 capillaries each in ≥10 terminal villi in ≥10 non-infarcted areas, (d) (100x) Sections from hemorrhagic areas showing ischemic necrosis

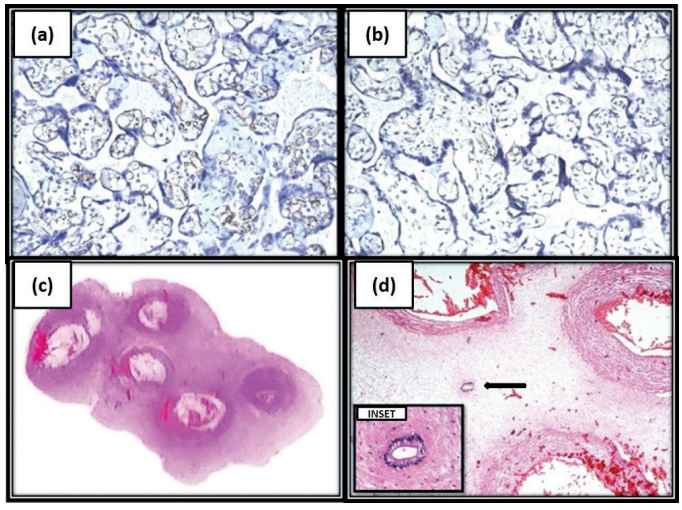

Figure 2. (a) (200x) Immunohistochemically stained capillary endothelial cells showed uniform positivity with CD34, demonstrating more capillaries than were easily discernible by hematoxylin-eosin stain, (b) (200x) Stain for smooth muscle actin was negative, (c) Sections from umbilical cord showing 5 blood vessels; 4 arteries and 1 vein and (d) (40x) an omphalomesenteric duct remnant is seen in between the blood vessels. INSET (400x) shows omphalomesenteric duct remnant

Discussion

Chorangiosis is a very rare entity found in 5-6% of placentas[2]. Its incidence increases with gestational age with more cases found in late preterm (32 to 37 weeks) and term (>37 weeks) pregnancies[1,2]. Its presence has been correlated with fetal morbidity and mortality and congenital malformations as high as 42% and 39%, respectively[1].

The proposed pathogenetic mechanism of chorangiosis is that chronic hypoperfusion or tissue hypoxemia causes elaboration of vascular endothelial growth factor, platelet-derived growth factor, and transforming growth factor-β by mesenchymal and trophoblastic cells[3]. An alternative hypothesis highlighting the role of macrophage-derived tumor necrosis factor-α has also been suggested[3]. Increased intramural pressure due to umbilical vein obstruction is also thought to play a role in the development of chorangiosis in cases associated with cord anomalies, such as long umbilical cord and thrombosis of vessels[3].

Chorangiosis is a histopathologic diagnosis. It must be differentiated from placental congestion, tissue ischemia,

chorangioma and chorangiomatosis[3,4]. In placental congestion, the vasculature is numerically normal. In tissue ischemia, there is shrinkage of the villi. Chorangioma is a well-circumscribed mass of solitary or multiple nodules. On microscopy, it is comprised of capillary-sized vascular channels with a mixture of endothelial cells, stromal cells, and surrounding trophoblasts. Chorangiomatosis is a heterogeneous, less well-defined lesion with intermediate features between chorangioma and chorangiosis. It has hyperplastic capillaries surrounding larger vessels in the central core of stem villi with increased numbers of loose, poorly cohesive lattices of perivascular bundles of reticulin fibers and circumferential layers of pericytes. These pericytes stain positively for SMA. Also, both chorangioma and chorangiomatosis are seen before 32 weeks of gestation and involve more proximal elements of villous structures, whereas chorangiosis is more common in late preterm and term pregnancy, and is a diffuse process involving the terminal villi.

Its etiology is poorly understood, but it has been found to be associated with various maternal and fetal disorders[1]. Placental disorders such as placentomegaly, chronic villitis, acute chorioamnionitis, amnion nodosum, and placenta previa have also been reported in association with chorangiosis[1,3]. However, contrary to Altshuler's initial description, it is now suggested to be associated with much improved pregnancy outcomes. Recently in 2016, Stanek reported that chorangiosis is an adaptive and protective mechanism against in utero hypoxia, and abnormal pregnancy outcomes are not a consequence of chorangiosis per se[1]. In 2017, Petersen et al.[5] concluded that chorangiosis is a placental marker of antepartum chronic low-grade hypoxia. In the present case study, the patient had gestational hypertension, oligohydramnios, and delivered a preterm stable child. The indication for cesarean section was decreased fetal heart rate with fetal distress, which might have been be due to chronic hypoxia resulting from pre-eclampsia.

Also, in the present case, an association of chorangiosis with a multiple vessel umbilical cord, having 5 blood vessels with an omphalomesenteric duct remnant was identified. Abnormalities that lead to multiple vessels in the cord are rare with the majority of the reported cases highlighting four vessels due to a persistent right umbilical vein[6]. However, occasional case reports mention five or more vessels in the cord in association with conjoined twins[6]. The child in the present case had no congenital anomalies. Also, the literature regarding their possible mechanism of occurrence and significance is sparse.

The omphalomesenteric (vitelline) duct connects the midgut lumen with the yolk sac in the developing fetus. It is often associated with remnants of vitelline vessels, seen in about 7% of umbilical cords[7]. Microscopically, they are lined by cuboidal to columnar epithelium with an intestinal phenotype and may have a surrounding smooth muscle layer.

To conclude, chorangiosis is an important histopathologic sign of fetal injury. It is an adaptive response to in-utero hypoxia and its presence signifies better pregnancy outcomes. To the best of our knowledge, this is the first case report to document the association of chorangiosis with a 5-vessel umbilical cord, whose presence does not always herald an adverse perinatal outcome, and an omphalomesenteric duct remnant.

Ethics

Ethical Committee Approval: The study was approved by ethical committee of the institute.

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

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Concept: P.D., Design: P.D., N.G., Data Collection or Processing: N.G., S.A., Analysis or Interpretation: P.D., N.G., Literature Search: N.G., S.A., J.H.G., Writing: N.G., P.D.

Conflict of Interest: There is no conflict of interest among the authors.

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Case Report / Olgu Sunumu

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Turk J Obstet Gynecol 2018;15:273-6

Prenatal detection of Peters plus-like syndrome

Peters-plus benzeri sendromun prenatal tanısı

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Abstract

Peters plus syndrome is a rare congenital disorder that includes ocular anterior segment defects of the classic Peter's anomaly, and is mostly associated with craniofacial and skeletal defects. A 21-week fetus was referred for further evaluation due to a suspicion of fetal hydrocephalus. An ultrasound examination revealed hyperechogenic lenses, microphthalmia, hypotelorism, retrognathia, mild ventriculomegaly, absence of the cavum septum pellucidum, and short stature. Amniocentesis and further microarray analysis revealed normal chromosomal copy numbers including the gene *B3GALTL*. In utero mort fetalis occurred at the 23rd gestational week. Ultrasound and fetal autopsy findings were suggestive of Peters plus syndrome, but the absence of the *B3GALTL* gene mutation made the diagnosis Peters plus-like syndrome. Obstetricians should consider Peters plus-like syndrome with prenatal detection of ocular anomalies along with craniofacial and skeletal anomalies with the absence of *B3GALTL* gene mutation.

Keywords: Peters anomaly, Peters plus syndrome, prenatal diagnosis, congenital cataract, *B3GALTL* gene

Öz

Peters-plus sendromu, klasik Peters anomalisinin oküler anterior segment defektlerini içeren ve çoğunlukla kraniyofasiyal ve iskelet defektleri ile ilişkili nadir görülen bir konjenital bozukluktur. Yirmi bir haftalık bir fetüs, fetal hidrosefali şüphesi nedeniyle ileri tetkik için sevk edilmiştir. Ultrasonografik değerlendirmede, hiperekojen lensler, mikroftalmi, hipotelorizm, retrognati, hafif ventrikülomegali, cavum septum pellucidum yokluğu ve boy kısalığı izlendi. Amniyosentez ve ileri mikroarray incelemesi, gen *B3GALTL* de dahil olmak üzere normal kromozomal kopya sayılarını tespit etti. Yirmi üçüncü gebelik haftasında fetal ölüm gerçekleşti. Ultrason ve fetal otopsi bulguları Peters-plus sendromuna işaret etmekteydi, fakat *B3GALTL* gen mutasyonunun olmaması Peters-plus benzeri bir sendromun tanısını koydurdu. Oküler anomalilerin prenatal tespiti durumunda beraberinde kraniofasiyal ve iskelet anomalilerinin bulunması ve *B3GALTL* gen mutasyonu bulunmayan durumlarda, obstetrisyenler Peters-plus benzeri sendromu hatırlamalıdırlar.

Anahtar Kelimeler: Peters anomalisi, Peters-plus sendromu, prenatal tanı, konjenital katarakt, *B3GALTL* geni

Introduction

Peters' anomaly is a rare congenital ocular anomaly caused by defective dysgenesis and cleavage of the anterior chamber of the eye causing central corneal opacity (leukoma), absence of the posterior corneal stroma and Descemet membrane, and a variable degree of iris and lenticular attachments to the central aspect of the posterior cornea[1]. Peters plus syndrome, previously known as Krause-Kivlin syndrome or Peters' anomaly with short-limb dwarfism (OMIM ≠ 261540), is an autosomal-recessive inherited congenital disorder caused by a mutation in the *B3GALTL* gene on chromosome 13q12.3. Peters plus syndrome is a rare anomaly with unknown incidence, with equal sex ratio, and a high incidence of consanguinity. Just over 70 cases have been reported in the postnatal period and 8 cases in the prenatal period[2-6]. The classic triad of Peters plus syndrome includes anterior segment defects (100%), short stature (100%), and brachydactyly (95%)[7]. There are also Peters plus-like syndromes, which did not carry a mutation in the *B3GALTL* gene, but have similar anomalies to the classic Peters-plus syndrome[8].

Herein, we report the prenatal diagnosis of Peters plus-like syndrome in a Turkish family without the *B3GALTL* gene mutation.

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Case Report

A 23-year-old woman, gravida1 partus 0, was referred to our clinic at the 21st week of her pregnancy due to the suspicion of fetal hydrocephalus. The fetal biometry scan showed appropriate biometric measurements, but long bone measurements, including femur, fibula, radius, and ulna were one week shorter than the expected gestational age. The detailed scan showed a female fetus with moderate ventriculomegaly, absence of the cavum septum pellucidum, a dilated third ventricle (Figure 1), echogenic lenses (Figure 2), retrognathia (inferior mandibular angle <50°), hypotelorism (binocular distance at 5th percentile and inter-ocular distance at 50th percentile), and microphthalmia (ocular diameter <5th percentile) (Figure 2).

Karyotyping and fetal magnetic resonance imaging (MRI) were scheduled owing to findings related to a chromosomal anomaly or a syndrome. Fetal MRI showed agenesis of the corpus callosum, ventriculomegaly, hypotelorism, and bilateral congenital cataracts. Amniocentesis and further karyotyping showed 46, XX chromosomes. Intrauterine fetal death occurred at the 23rd gestational week. A 500-gram female fetus was delivered vaginally after cervical preparation and proper induction. Pathologic autopsy showed narrow palpebral fissures, a long philtrum, cupid's bow upper lips with a thin vermilion border, and facial hirsutism and low-set ears (Figures 3 and 4), bilateral absence of corneal endothelium and Descemet membrane, bilateral optic nerve degeneration (Figures 5 and 6), bilateral cataracts, agenesis of the corpus callosum, and hydrocephalus.

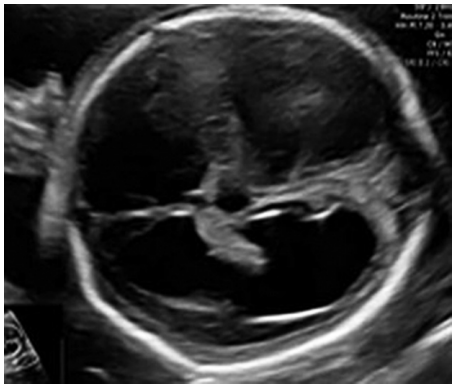

Figure 1. Hyperechogenic patterns of the lens and anterior chamber

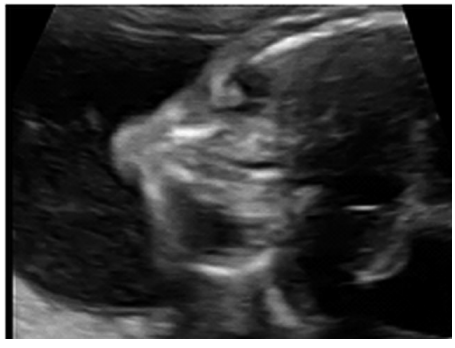

Figure 2. Binocular distance was 29 mm (5th percentile), inter-ocular distance was 13.5 mm (50th percentile) and ocular diameter 7.6 mm (<5th percentile) (microphthalmia) at 21 weeks

The autopsy council, including ophthalmologists, confirmed the diagnosis of Peters plus syndrome. The parents were not consanguineous, and their relatives did not indicate a history of such anomalies. Further microarray analyses [Affymetrix, *GRCh37* (*hg19*)] revealed normal chromosome copy numbers. Analysis of the genes *PAX6* (*11p13*), *PITX2* (or *RIEG1*) (*4p25-26*), *PITX3* (RIEG/PITX homeobox gene family) (*10q25*), *CYP1B1* (cytochrome *P4501B1* gene) (*2p22*), *FKHL7* (Forkhead transcription factor) and *B3GALTL* gene (*13q12.3*) revealed no deletions or duplications in these genes. DNA sequencing would inform us about specific point mutations of these genes that have the potential to play a role in Peters plus syndrome. However, due to the scant amount of DNA in our sample, we could not perform detailed sequencing of these genetic regions.

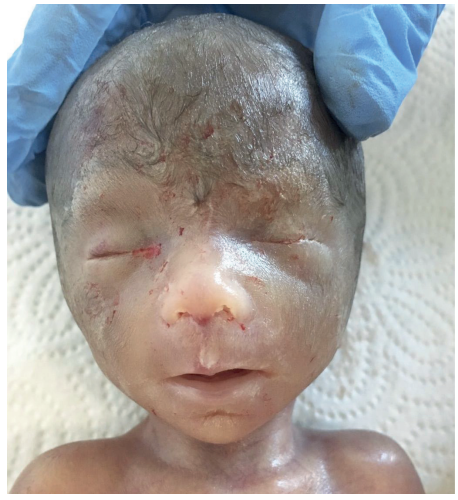

Figure 3. Fetal face: note the narrow palpebral fissures, a long philtrum, cupid's bow upper lips with a thin vermillion border

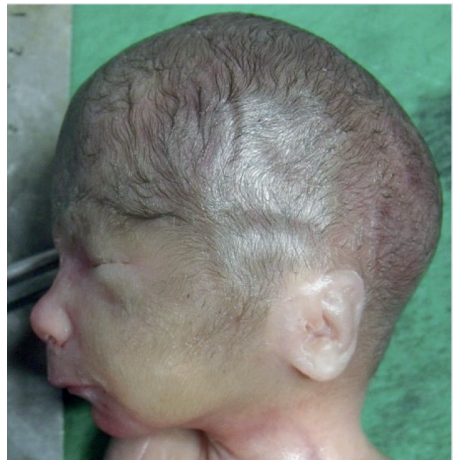

Figure 4. Fascial profile: fascial hirsutism and low-set ears

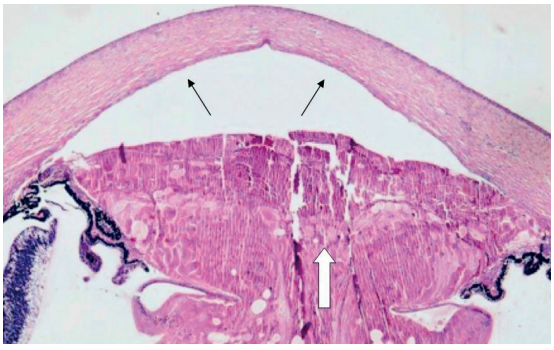

Figure 5. Absence of the posterior corneal stroma and Descemet membrane (black arrows), protrusion of the lens material to the anterior chamber (white arrow)

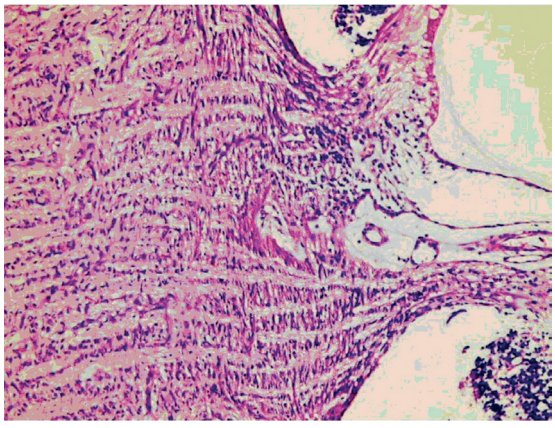

Figure 6. Optic nerve degeneration

Discussion

If typical ocular anomalies of Peters' anomaly accompany with additional malformations, this situation is referred to as Peters plus syndrome. Peters plus syndrome was initially understood as a causally heterogeneous morphologic entity[2,3]. It is now a well-defined syndromic disorder, being confined to a narrower spectrum of accompanying malformations and being related to homozygous or compound heterozygous *B3GALTL* mutations[7]. However, other syndromes with a Peter's anomaly do not fulfill the criteria of Peters plus syndrome.

The clinical features of Peters plus syndrome includes a prominent forehead, narrow palpebral fissures, a long philtrum, cupid's bow upper lips, cleft lip and palate, preauricular ribs, micrognathia, a broad neck, cataracts and glaucoma, short limbs, brachydactyly, clinodactyly, microcephaly, brain atrophy, agenesis of the corpus callosum, and variable developmental delay and intellectual disability. Some of these features may be present prenatally or at birth, and some may occur at later ages[2].

In contrast to other prenatally detected Peters plus syndrome cases, our case did not show a *B3GALTL* gene mutation. In prenatally detected cases of Peters plus syndrome, including our case, no *B3GALTL* gene mutation has been reported to date[5,9]. There may be some explanations for this situation; these cases may be a variant or a phenotypic overlap of Peters plus syndrome[8] or these cases may carry a distinct mutation, which needs further investigation. We also analyzed various mutations in genes that were shown to be linked to the ocular anomaly of Peters' syndrome or involved in eye development (*PAX6, PITX2, PITX3, CYP1B1, FKHL7*), and no mutations were observed in these genes either. In this situation, our case is more suitable for defining as Peters plus-like syndrome.

Prenatal detection of Peters plus syndrome and like syndromes require a handful of dedicated physicians, including obstetricians, ophthalmologists, genetic specialists, and pathologists. In particular, obstetricians and ultrasonographers should pay attention to the eye, and if ocular anomalies are suspected, craniofacial and skeletal system and fetal growth monitoring should be remembered for the prenatal detection of Peters plus syndrome. In the differential diagnosis of Peters plus syndrome, similar syndromes such as SHORT, Abbruzo-Erickson, GMS, Weill-Marchesani, Michels, Rieger, Walker-Warburg, Cornelia de Lange, Robinow, and fetal alcohol syndrome can be detected according to Orphanet data (http:77www.orpha.net).

Herein, we report a case of Peters plus-like syndrome that was prenatally detected in a patient from Turkey with no family history. The diagnosis was made solely through prenatal ultrasound despite normal fetal chromosomes and no mutation in the *B3GALTL* gene in this sporadic case.

As a result, in cases of fetal anterior segment defects, obstetricians should remember Peter's anomaly, Peters plus syndrome, and Peters plus-like syndrome, and they should also scan for other accompanying features of these diseases, and perform prenatal invasive tests, including specific gene mutations.

Ethics

Informed Consent: Informed consent acquired from the patient to publish this case report.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.T.C., L.D.Ç., N.D., Concept: M.T.C., N.D., Design: A.B.D., N.D., Data Collection or Processing: L.D.Ç., A.B.D., N.D., Analysis or Interpretation: L.D.Ç., A.B.D., Literature Search: M.T.C., N.D., Writing: M.T.C., N.D.

Conflict of Interest: The authors declare no conflict of interest.

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

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Letter to the Editor / Editöre Mektup

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Turk J Obstet Gynecol 2018;15:277-8

Inhibitory kappa B alpha expression in endometriosis

Endometrioziste inhibitör kappa B alfa ekspresyonu

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Keywords: Endometriosis, endometriotic implants, deep infiltrating endometriosis, inhibitory kappa B
Anahtar Kelimeler: Endometriozis, endometriotik implantlar, derin infiltran endometriozis, inhibitor kappa B

To the Editor,

We read with great interest the article by Arlier et al.[1] entitled "Tumor necrosis factor alfa and interleukin 1 alfa-induced phosphorylation and degradation of inhibitory kappa B (IκB), alfa are regulated by estradiol (E_2) in endometrial cells," published in your journal. Interestingly, the authors demonstrated that ectopic endometrium was significantly characterized by less immunoreactivity for IκB, a cytoplasmatic inhibitor of the transcription factor nuclear factor (NF)-κB, and that E_2 might modulate its expression. The rational of this study is based on evidence of the critical role of NF-κB, which mediates gene transcription of several protein involved in inflammation, angiogenesis, as well as in proliferation and reduced apoptosis of endometriotic cells. A previous study reported that an excessive activation of NF-κB might be present in endometriotic implants of women affected by endometriosis[2]. For this reason, it might represent an interesting target for treating this benign chronic hormonal-dependent disease[3]. Although the authors should be congratulated for their laboratory findings, we would like to discuss some methodologic concerns of their study. In the material and methods, the authors described that the ectopic endometrial samples for western blot and immunocytochemical analysis were obtained from 6 women with endometriosis. First, the authors should add information on the severity of endometriosis for each patient in accordance with American Society of Reproductive Medicine classification. More importantly, the authors did not report from which sites the endometriotic implants were obtained, and in particular, if they originated from peritoneal nodules, ovarian endometriomas or deep infiltrating endometriosis (DIE) nodules. In general, it would be of particular interest to know if the activity of IκB and the effect of E_2 on its expression would be different in implants originating from these three distinguished phenotypes of endometriosis, which probably have different pathogeneses[4]. Regarding this aspect, it has been previously described that nodules of DIE may have higher proinflammatory reaction, higher vascularization, as well a higher density of nerve fibers, which may be responsible for a more aggressive clinical behavior[5]. Nevertheless, the results of the study by Arlier et al.[1] are innovative and promising. Thus, in the near future, new studies are needed to better clarify the role IκB in inflammatory pathway of endometriotic cells. More importantly, it could be advisable to better understand if this protein may represent a suitable molecular target for a chronic medical therapy, which needs to balance clinical efficacy with cost and tolerability.

Ethics

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.F., Concept: F.B., S.F., Design: F.B., S.F., Data Collection or Processing: F.B., C.S., S.F.,

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Conflict of Interest: The authors reported no conflicts of interest.

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Letter to the Editor / Editöre Mektup

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Turk J Obstet Gynecol 2018;15:279-80

Leiomyomatosis peritonealis disseminata in a nonpregnant woman

Nulligravid olguda leiomyomatosis peritonealis disseminata

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Keywords: Nulligravida, leiomyomatosis peritonealis disseminata, abdominal mass
Anahtar Kelimeler: Nulligravid, leiomyomatosis peritonealis disseminata, abdominal kitle

To the Editor,

Leiomyomatosis peritonealis disseminata (LPD) is a rare entity characterized by the presence of multiple, small nodules of smooth muscle on the peritoneal and omental surfaces[1]. LPD was first described by Wilson and Peale in 1952. Fewer than 140 cases have been reported so far[1,2]. It is generally seen in women at reproductive ages; however, there are cases reported in men[2]. In most cases, there is an underlying condition such as pregnancy or exogenous hormone replacement, which may cause elevated estrogen levels[3]. Here, we present a case of LPD, which developed in a nulligravida woman who received no exogenous hormone therapy. A nulligravida women aged 36 years presented to the gynecology department of İstanbul Göztepe Training and Research Hospital with lower abdominal pain, which she had had for over a year. In her history, there was no history of chronic disease or drug use. She had regular menstrual cycles. In the laboratory evaluation, cancer antigen (CA)-125 was 43.9 U/mL and serum estradiol and progesterone levels were within normal range. A computed tomography scan revealed a mass lesion, which filled the pelvis completely and extended to the peritoneum. Thus, she underwent a laparotomy for removal of the mass lesion. In the laparotomy, a multi-nodular, solid mass lesion originating from the anterior serosal surface of the uterus was seen (Figure 1A, B). Both adnexa were unremarkable. In addition, multiple, solid nodules (2 or 3 cm in size) were present over the peritoneum. There was diffuse, free fluid in abdomen. Mesenchymal neoplasm was primarily considered in the patient who desired to preserve fertility, and therefore a frozen examination was not performed. Fertility was preserved and only excision of masses over the peritoneum and originating from the anterior serosal surface of uterus was performed. Gross pathology showed a multi-nodular mass lesion (30x24x8 cm in size) that consisted of multiple, fibrillary nodules with a creamy-white appearance. On microscopic examination, there were bland smooth muscle cells resembling ordinary leiomyoma without atypia, necrosis or mitosis (Figure 1C, D). Tumor cells were reactive for estrogen receptor, progesterone receptor, desmin, alpha smooth muscle actin, and caldesmon (Figure 1E, F). The Ki-67 index was <1. No S-100, AE1/AE3, cam 5.2 or CD117 expression was observed in the tumor cells. Histopathologic and immunohistochemical findings favored smooth muscle tumor.

LPD is a rare lesion that is mainly seen in young-middle aged women who have hormonal changes due to pregnancy[2,3]. Although its pathophysiology is not fully understood, it may be classified in 4 categories including hormonal, iatrogenic, genetic, and subperitoneal mesenchymal cell metaplasia. Although some authors suggest that it arises from subserosal cells with myofibroblastic or smooth muscle cell metaplasia, Travassoli and Norris support the hormonal theory given that most patients are pregnant women or have a history of long-term oral contraceptive use, and that tumor cells express estrogen and progesterone receptors[4]. The vast majority of

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patients are asymptomatic; however, non-specific findings such as abdominal pain, vaginal bleeding or intestinal obstruction caused by the mass lesion may be present in symptomatic patients. We believe that the number of patients with LPD is underestimated in the literature because most cases are asymptomatic[3].

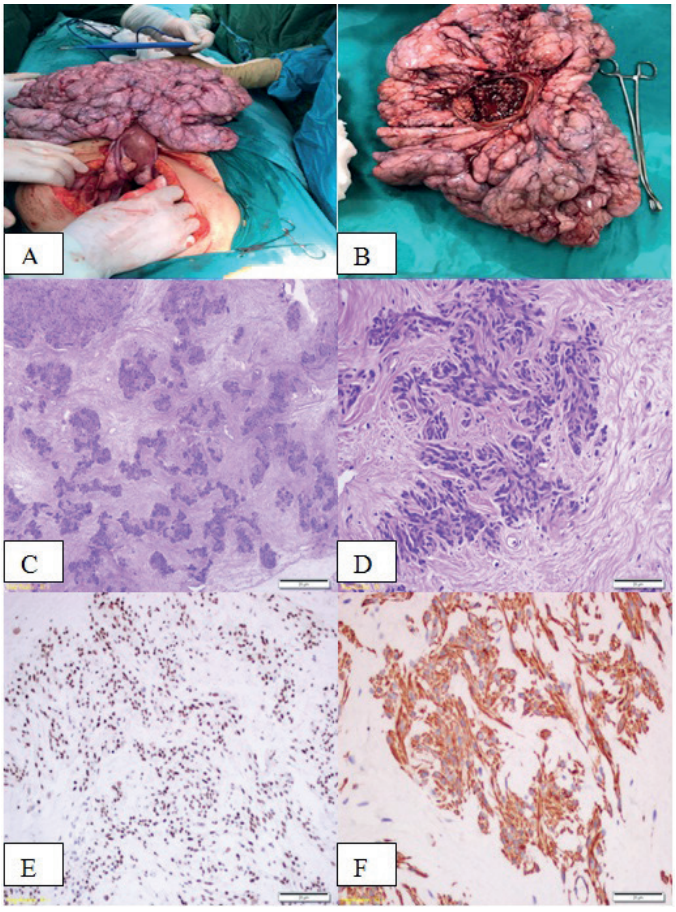

Figure 1. A-F) Intraoperative photography showed multinodular solid mass that had originated from anterior serosal surface of uterus (A, B), microscopic examination revealed smooth muscle proliferation (hematoxylin and eosin Cx40, Dx200), estrogen receptor and caldesmon positivity in tumor cells (E and F x200)

In conclusion, in the differential diagnosis of this entity, peritoneal carcinomatosis and leiomyosarcoma should be considered[5]. In our patient, peritoneal carcinomatosis was excluded by histopathologic findings and the absence of primary carcinoma, and leiomyosarcoma was excluded because of the lack of atypia, pleomorphism, necrosis, and high mitotic index[2]. LPD is a tumor with benign course in general, although there have been a few cases with malignant transformation[4,5].

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.K., M.P., Concept: A.A., T.S., Design: A.A., A.K., Data Collection or Processing: T.S., B.R.G., Analysis or Interpretation: A.A., T.S., Literature Search: A.A., T.S., Writing: A.A., T.S., B.R.G.

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ERRATUM

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The title of the article has been corrected as following:

Use of a gelatin-thrombin hemostatic matrix in obstetrics and gynecological surgery

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