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Clinical Investigatio

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TURKISH JOURNAL OF OBSTETRICS AND GYNECOLOGY

AIMS AND SCOPE

Turkish Journal of Obstetrics and Gynecology (formerly called Türk Jinekoloji ve Obstetrik Derneği Dergisi) is the official peer-reviewed journal of the Turkish Society of Obstetrics and Gynecology and is published quarterly on March, June, September and December.

It is an independent peer-reviewed international journal published in English language since 2014 September. Manuscripts are reviewed in accordance with "double-blind peer review" process for both referees and authors.

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

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appropriately investigated and resolved. The statement about the authors' contributions should be placed in the cover letter. All persons who contributed to the work, but not sufficiently to be authors, must be acknowledged.

Cover Letter

Cover letter to the editors addressing the following points:

· The authors' intent to submit solely to Turkish Journal of Obstetrics and Gynecology.

· Verification that the manuscript is not under consideration elsewhere, and indication from the authors that it will not be submitted elsewhere until a final decision is made by the editors of Turkish Journal of Obstetrics and Gynecology.

· The declaration of transparency from the corresponding author.

· Clinical trial registration, if applicable.

· Institutional review board (IRB) approval or exemption.

· Informed consent.

· Any explanations related to reporting guidelines.

· The statement about the authors' contributions.

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The "Turkish Journal of Obstetrics and Gynecology" follows the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" (International Committee of Medical Journal Editors - http://www.icmje.org/). Upon submission of the manuscript, authors are to indicate the type of trial/research and provide the checklist of the following guidelines when appropriate:

CONSORT statement for randomized controlled trials (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel group randomized trials. JAMA 2001; 285: 1987-91) (http://www.consort-statement.org/),

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CARE guidelines are designed to increase the accuracy, transparency, and usefulness of case reports. (Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D; the CARE Group. The CARE Guidelines: Consensus-based Clinical Case Reporting Guideline Development.) (http://www.care-statement.org/)

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

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

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All manuscripts must be submitted as Microsoft Word (.doc or .docx) files. All manuscript pages (including references, tables, and figure legends) must be double-spaced. Use a standard, 12-point typeface such as Times New Roman. Top, bottom, and side margins should be set at 1 inch. Authors must include the following in the manuscript file:

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Title Page

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.

Several types of articles can be submitted for publication in Turkish Journal of Obstetrics and Gynecology: Original research, case reports, systematic reviews, current commentaries, procedures and instruments, and letters. Stated word counts and page limits were shown in Table 1. Copyright transfer forms, the cover letter, and figures do not contribute to the page limits.

Table 1. Manuscript length at a glance

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

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

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."

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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:

Introduction, Case Report, Discussion and References.

References

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

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

Journal titles should conform to the abbreviations used in "Cumulated Index Medicus".

Examples

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

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

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

Tables and Figures

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Units of Measurement and Abbreviations

Units of measurement should be in Systéme International (SI) units. Abbreviations should be avoided in the title. Use only standard abbreviations. If abbreviations are used in the text, they should be defined in the text when first used.

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

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Accepted articles are provided with a DOI number and published as ahead of print articles before they are included in their scheduled issue.

Journal and Society Web sites:

www.tjod.org (Turkish Society of Obstetrics and Gynecology)

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TURKISH JOURNAL OF OBSTETRICS AND GYNECOLOGY

CONTENTS

Clinical Investigations

Case Report

CONTENTS

TURKISH JOURNAL OF OBSTETRICS AND GYNECOLOGY

LETTER FROM THE PRESIDENT

Dear Collagues,

We announce that we want to establish solidarity and cooperation among all the obstetricians and gynecologists by the season 2019-2020. We should not criticise our collagues severely against patients and give random information to patients in terms of medical practices. As the community of obstetrics and gynecology, all the collagues should support and help each other while executing our medical practices. We will work hard in collaboration to achieve such an aim; thus, we willl decrease the number of medical cases that we deal with.

I especially would like to thank the editors, the vice editors and the referees who worked hard for the journal throughout the year. I also want to thank our collagues who follow and support our journal.

I believe that we will maintain and develop the collaboration in the next years. I look forward to your contributions and support.

Sincerely,

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

TURKISH JOURNAL OF OBSTETRICS AND GYNECOLOGY

EDITORIAL

Dear Colleagues,

Our journal is now included Citefactor database. This database a free site to search and download which in concordance with our journals policy abour free circulation of scientific knowledge. Our 2018 impact factor in Web of Science is 0.376. The monthly view of our journal in PubMed Central has reached to 20 thousand in 2019 which will also help increase visibility of the research published in our journal. We look forward for your best research articles.

Gynecology Masterclass 2019 supported by our society has trained 240 specialists with theoretical lessons, video surgery and cadeveric dissection education. It has participants from five countries other than Turkey which is becoming an international venue to teach surgical anatomy, cosmetic gynecology, urogynecology, radical and reconstructive surgeries, advanced obstetric surgeries, laparoscopy and hysteroscopy. Our survey showed that more than 75% of the participants begin to apply a new surgical technique and 94% experienced an improvement of their surgical knowledge and technique.

Turkisy Society of Obstetrics and Gynecology decided to form an accreditation council. The aim is to form minimum standarts of obstetrics and gynecology education together with its subspecialities of Perinatology, Gynecological Oncology, Infertility and Urogynecology in accordance with European Board of Obstetrics and Gynecology. Also the first proficiency test will be held in the 2020 congress of Turkish Society of Obstetrics and Gynecology. Review articles published in our journal will be a source of several questions in our proficiency exam.

All the best.

Eray Calışkan
Editor in Chief

Clinical Investigation / Araştırma

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Female genital image: is there a relationship with body image?

Kadınların genital ve vücut görüntüsü arasında bir ilişki var mı?

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Abstract

Objective: Dissatisfaction with body image may extend to the genital region, and the most dissatisfied with their bodies are women. To analyze the relation between body image and genital image in female, and to verify demographic and/or clinical factors related to body image and genital image.

Materials and Methods: This is a cross-sectional study in 421 women. The Body Shape Questionnaire-34 (BSQ-34) was used to evaluate body image perception; scores ≤110 indicate no dissatisfaction. Also, the female genital self-image scale-7 (FGSIS-7) was used to evaluate genital self-image; scores range between 7 and 28, with higher values considered to indicate a more positive genital self-image. The relation between body image and genital image was determined using the Pearson Correlation test, as well as the relation of these with body mass index (BMI) and age. The relation between these data and genital image was determined by using the ANOVA test or the independent t-test (statistical difference was accepted as $p<0.05$). In order to verify predictors of dissatisfaction with body image, variables with $p<0.10$ were inserted into the logistic regression model and checked if they remained significant ($p<0.05$).

Results: Three hundred eighty-nine women were analyzed. The mean age was 34.7±10.2 years. The mean BMI was 24.1±3.6 kg/m², 49% were single, and the mean BSQ-34 and FGSIS scores were 83.2±30.8 and 23.8±3.4, respectively. The correlation (r=-0.24) was found between body image and genital image ($p<0.001$). A total of 315 women indicated to be satisfied with their body and presented an FGSIS-7 score of 24±3.3. Participants who were dissatisfied with their body had an average FGSIS-7 score of 22.6±3.3.

Conclusion: Genital image, age, and BMI influence body image. Change in the perception of body image seems to have low correlation with genital self-image in women.

Keywords: Body image, female genitalia, women, genital (self-)image

Öz

Amaç: Vücut görüntüsü ile ilgili memnuniyetsizlik genital bölgeye kadar uzanabilmektedir ve vücutlarından en çok memnuniyetsiz olanlar kadınlardır. Bu çalışmada, kadınlarda vücut görüntüsü ve genital görüntü arasındaki ilişkinin analiz edilmesi ve vücut görüntüsü ve genital görüntü ile ilgili demografik ve/veya klinik faktörlerin doğrulanması amaçlanmıştır.

Gereç ve Yöntemler: Dört yüz yirmi bir kadında kesitsel çalışma yürütülmüştür. Beden Şekli Anketi-34'te (BSQ-34) beden imajı algısında memnuniyetsizlik olmadığını gösteren puan ≤110 olarak alınmış; 7-28 arasında bir skor sistemine sahip olan kadın genital öz-imaj ölçeği-7'de (FGSIS-7) daha yüksek değerlerin daha pozitif bir genital öz-imajı gösterdiği düşünülmüştür. Birleşmiş görüntü ve genital görüntü arasındaki ilişki ile birlikte bunların vücut kitle indeksi (VKİ) ve yaş ile ilişkisi Pearson Korelasyon testi ile değerlendirilmiştir. Bu veriler ve genital görüntü arasındaki ilişki ANOVA testi veya bağımsız t-testi kullanılarak belirlenmiştir (buna karşın istatistiksel fark $p<0,05$). Vücut görüntüsü ile ilgili memnuniyetsizliğin öngörülerini doğrulamak için $p<0,10$ olan değişkenler lojistik regresyon modeline eklenmiş ve anlamlı olup olmadıkları kontrol edilmiştir.

Bulgular: Üç yüz seksen dokuz kadının ortalama yaşı 34,7±10,2 yıl, VKİ'si 24,1±3,6 kg/m², %49'u bekar olup; BSQ-34: 83,2±30,8 ve FGSIS-7: 23,8±3,4 olarak analiz edildi. Vücut görüntüsü ile genital görüntü arasında korelasyon bulundu (r=-0,24) ($p<0,001$). Toplam 315 kadının vücutlarından memnun kaldığı ve FGSIS-7 puanının 24±3,3 olduğu bildirildi. Vücutlarından memnun olmayan katılımcıların ortalama FGSIS-7 puanı 22,6±3,3 idi.

Sonuç: Genital görüntü, yaş ve VKİ vücut görüntüsünü etkilemektedir. Kadınlarda beden imajı algısındaki değişimin genital öz-imajı ile düşük korelasyona sahip olduğu görülmektedir.

Anahtar Kelimeler: Vücut görüntüsü, kadın genitalya, genital öz-imaj

PRECIS: The dissatisfaction with body image is associated with poorer genital self-image.

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Introduction

The dissatisfaction with body self-image in the Brazilian adult population is around 60 to 87%. In a general way, women are the most dissatisfied with their bodies, and being overweight was the main reason for body dissatisfaction[1-4]. Dissatisfaction in relation to one's own body may affect one's health in various ways, for example in a psychosocial and/or nutritional way, or in behavior towards the practice of physical activities, sexual health, as well as the search for esthetic procedures[1,5,6].

Women's perception of body image may extend to different parts of the body, including their intimate region[7,8]. Attention to the external genitalia has grown in parallel with pubic hair depilation tendencies, which results in a greater exposure of the sexual organs[9,10]. As genitalia are more exposed, the degree of satisfaction with external genital organs can be influenced, as well as women's sexual experiences[11,12].

In Brazil, body exposure and body image are highly valued by men and women due to strong socio-cultural influences[13]. However, it is still unknown if there is a relation between the cult of the body and female genital image. What could be observed is that Brazilian women, who undergo many esthetic body procedures, also perform innumerable surgeries in the genital region. In the last survey conducted by the International Society of Aesthetic Plastic Surgeons (ISAPS) in 2014, it was possible to observe that Brazil was the country where the most genital esthetic surgeries were performed. Moreover, this surgery was one of the most performed in the country[14]. Just as in Turkey, the main motivator for labiaplasty was found as improvement in genital appearance integrated with their esthetic and sexual demands[15].

In the literature, we found studies that verified the relation between body-image and female genital image in a university population, and in women with dyspareunia[8,16]. However, the relation between the level of satisfaction of Brazilian women with genital self-image is not well defined. The objective of this study was to analyze the relation between body and genital image, as well as to verify demographic and/or clinical factors related to them.

Materials and Methods

This is a cross-sectional study. Adult women recruited at health promotion events conducted by the Pelvic Floor Care Center in the cities of Salvador-Bahia in Brazil were invited to participate in the survey from February to June 2015. Seventy women aged between 18 and 60 years who were members of health clubs were included in the study. Pregnant volunteers and those who did not complete the submitted assessment instruments were excluded from the research.

Procedures of data collection

The volunteers were informed about the study objectives by previously trained researchers. After expressing an interest in participating, they were directed to a separate place and given instructions to complete the self-administered questionnaires individually. The research was conducted using evaluation instruments to collect socio-demographic and clinical information, the Body Shape Questionnaire (BSQ-34) and the female genital self-image scale (FGSIS-7).

Evaluation tools

Body image

The BSQ-34 is an instrument that was validated for use in the Portuguese language by Di Pietro & Silveira, in 2009. It consists of 34 questions and was developed to measure concerns of body image and weight over the previous four weeks. The tool provides an evaluation on body image dissatisfaction in clinical and research environments[17].

The questions refer to the degree of concerns with body shape and weight, self-depreciation related to clinical appearance, and behavioral modifications. The answers have scores ranging from one to six, representing the options: never, rarely, sometimes, often, very often, and always, respectively. The final score can range from 34 to 204 points, with a value less than or equal to 110 indicating no concerns, a value greater than 110 and less than or equal to 138 indicating mild concern, a score greater than 138 and less than or equal to 167 corresponding to a moderate concern, and a score greater than 167 is indicative of serious bodily concern[18].

Genital image

The assessment of satisfaction and women's beliefs regarding their own genitalia was performed by using the FGSIS-7. This is a reliable questionnaire consisting of seven questions with a four-point answer scale in descending order (i totally agree, agree, disagree, strongly disagree). The seven items in the questionnaire include smell and taste, appearance, sexual function, shame, and pride. The total score can range from 7 to 28 points, there is no cut-off point, and higher scores indicate a more positive self-image of the genitalia[12].

Herbenick et al.,[12] recommended that the absence of a response justified the exclusion of the analysis from the scale. The FGSIS-7 has been translated and validated for some Western and Eastern countries and is considered a reliable measurement tool[19-22]. To date, the instrument has not been validated in Brazil, but it is in the process of validation. The authors translated the scale because no other validated scale or questionnaire was found to assess genital self-image.

Statistics

The correlation variables corresponded to the BSQ-34 questionnaires and to FGSIS. The correlation variables corresponding to the BSQ-34 questionnaires provided a numeric variable, and scores less than or equal to 110 were considered to indicate body image satisfaction because of an absence of concerns related to the body[18]. FGSIS-7 provides

a numerical variable in which higher values represent a more positive genital self-image[19].

If the body mass index (BMI) is less than 18.5 kg/m^2, it falls into the underweight range. If the BMI is 18.5 to <25 kg/m^2, it falls within the normal range. If the BMI is 25.0 to <30 kg/m^2, it falls within the overweight range. If the BMI is 30.0 kg/m^2 or higher, it is regarded as obesity.

In order to derive the sample size of this research, the Winpepi calculator was used, through the ETCETERA command (miscellaneous procedures) in order to obtain a sample size through the correlation coefficient. The parameters were: correlation coefficient 0.2[16,19] and a power of 80% with a significance of 5%, obtaining n of 194 participants, adding 10% of possible losses, and 214 individuals in the aggregate.

Statistical Analysis

In order to prepare the database and descriptive analysis, the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA), version 14.0 for Windows was used. The normality of the numeric variables was examined through descriptive statistics, graphical analysis, and the Kolmogorov-Smirnov test. The correlation between the scores of BSQ-34 and FGSIS-7 questionnaires was evaluated by means of Pearson's correlation, as well as the correlation with age and BMI. For the purpose of comparison of categorical variables (BSQ-34 categorical vs. schooling, marital status, medication-hormone use, type of delivery and previous pelvic surgery), the chi-square test was used. In order to compare the means between categorical BSQ-34 with FGSIS-7, age and BMI, the independent t-test was used.

The multiple logistic regression model was used to evaluate the possibility to predict each independent variable in case of a change in body image using the BSQ-34. The multiple logistic regression model was used to evaluate the predictive ability of each independent variable in a change in outcome regarding body image using BSQ-34. After the univariate analysis, the variables were inserted into the logistic model if $p<0.10$, and they were kept in the model if they remained significant ($p<0.05$). The manual procedure for insertion and withdrawal of the variables was adopted. The power of discrimination of the model was determined using the area under the receiver operating characteristics (ROC) curve, represented by the C statistic, allowing to define the capacity to discriminate those with and without body alterations. The calibration of the model was verified using the Hosmer and Lemeshow test.

This study was approved by the Research Ethics Committee of the Bahia School of Medicine and Public Health, where it received the following CAAE number: 14425813.9.0000.5544. All patients signed the Free and informed consent form.

Results

The sample comprised 387 women. Initially, 423 volunteers participated in this study, with a loss of 35 participants because they did not complete the BSQ-34 questionnaire and one for not completing the FGSIS-7. Table 1 describes the socio-demographic and clinical data of the sample.

A negative and weak correlation was identified between the BSQ-34 and FGSIS-7 questionnaires, with a correlation coefficient of -0.240 ($p<0.001$), whereby the higher the body satisfaction the better the perception of the genital self-image. The women in this study were divided into two groups: those who were satisfied and dissatisfied with their body image. When comparing the FGSIS-7 score between these two groups, it was observed that women who were dissatisfied with their body presented a worse genital image, derived from

Table 1. Socio-demographic and clinical characteristics of 387 women

Variables	Mean ± SD
Age (years)	34.7±10.2
BSQ-34	83.2±30.8
FGSIS-7	23.8±3.4
Civil status	**n** (%)
Single	190 (49)
Married	175 (45.3)
Divorced	19 (4.9)
Widow	2 (0.5)
Education	**n** (%)
Secondary school	32 (8.2)
Not completed higher education	74 (19)
Higher education completed	283 (72.8)
BMI (kg/m²)	**n** (%)
Underweight	4 (1.1)
Normal range	252 (67.7)
Over weight	91 (24.5)
Obesity	25 (6.7)
Gestation, number of births	n (%)
Nulliparous	203 (53.8)
Primiparous	58 (15.4)
Multiparous	116 (30.8)
Medicines	n (%)
Use of hormones	231(71.3)
Menopause	n (%)
Yes	52 (13.4)
Genital surgery	n (%)
Yes	15 (4.2)

SD: Standard deviation, n: Number of participants, BMI: Body mass index
BSQ: Body shope Questionnaire, FGSIS: Female genital self-image scale

a lower score in the evaluation instrument (p=0.002). In the comparison of the means of clinical and socio-demographic data, it was verified that women who were dissatisfied with their body presented a higher BMI and lower age (p<0.05). The data are presented in Table 2.

Analysis of predictors of body image with genital image and socio-demographic and clinical data showed that female genital self-imaging, age, and BMI influenced body image (p<0.05) (Table 3). The ROC curve was used to represent the relationship between age, BMI, and FGSIS with body image.

Table 2. Comparison of body image (BSQ-34) with the genital image (FGSIS-7) and demographic and clinical variables of women

Variables	Dissatisfied with body image n=72 (19%) mean ± SD	Satisfied with body image n=315 (81%) mean ± SD	p value
FGSIS-7	22.7±3.4	24.0±3.31	0.002*
BMI	26.7±4.3	23.6±3.2	<0.001*
Age	32.1±9.7	35.3±0.2	0.019*
Civil status	**n (%)**	**n (%)**	
Single	39 (55.7)	151 (48.1)	0.5
Married	29 (41.4)	144 (45.9)	
Divorced	2 (2.9)	19 (6.0)	
Education			
Higher education completed	46 (63.9)	235 (74.6)	0.2
Not completed higher education	17 (23.6)	57 (18.1)	
Secondary school	09 (12.5)	23 (7.3)	
Types of births			
No delivery	45 (63.4)	175 (56.5)	0.5
Cesarean	3 (4.2)	26 (8.4)	
Normal	21 (29.6)	95 (30.6)	
Cesarean and normal	2 (2.8)	14 (4.5)	
Medicinal hormone			
Yes	16 (26.7)	77 (29.2)	0.7
Menopause			
Yes	07 (10.1)	35 (11.4)	0.9
Pelvic surgery			
Yes	09 (12.7)	41 (13.2)	0.8

SD: Standard deviation, n: Number of participants, BSQ-34: Body Shape Questionnaire-34, FGSIS-7: Female genital self-image scale-7, BMI: Body mass index, *p<0.05 with the independent t-test

Through this final model, an ROC curve was developed that obtained an area of 0.79 (95% CI: 0.74-0.85), with p<0.001, as described in Figure 1.

Discussion

To date, studies that evaluate the relationship between body and genital image are scarce, and nonexistent in the Brazilian female population. In the present study, a correlation was verified between female body and genital images. Participants dissatisfied with their body image, due to concerns about their body, were more dissatisfied with their genital self-image. By examining the satisfaction between body and genital image in female university students, research revealed that women who were more satisfied with their genitalia were more satisfied with their body[7,16,19].

Pazmany et al.,[8] described the relation between body and genital image of a sample that was divided into two groups:

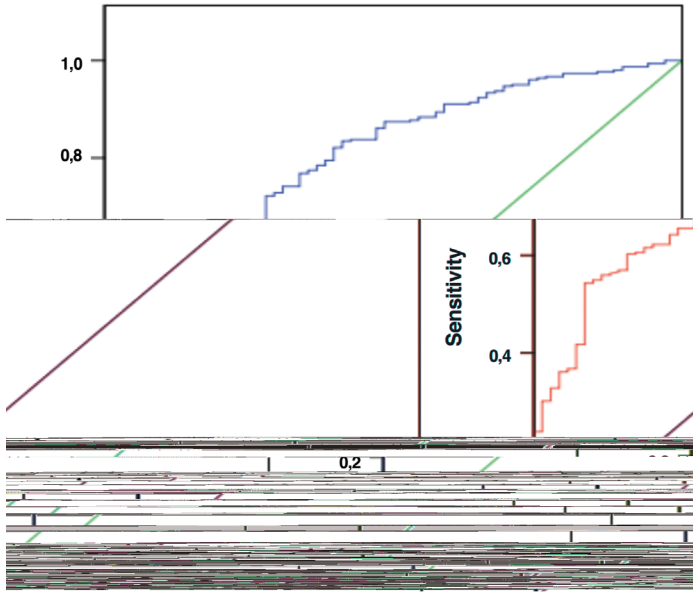

Figure 1. Area under the ROC curve of the final model (BMI, age and FGSIS) for body image

ROC: Receiver operating characteristic, BMI: Body mass index, FGSIS: Female genital self-image scale

Table 3. Independent variables of body satisfaction through the BSQ-34

	β-coefficient	Odds ratio CI (95%)	p value
Age	-0.1	0.9 (0.9-1.0)	<0.01
BMI	0.2	1.3 (1.2-1.4)	<0.01
FGSIS-7	-0.1	0.9 (0.8-1.0)	0.005

CI: Confidence interval, FGSIS-7: Female genital self-image scale-7, BMI: Body mass index, *p<0.05 with multiple logistic regression model, BSQ-34: Body shope Questionnaire-34

women with self-reported dyspareunia and a control group with women who did not report pain during or after sexual intercourse. When analyzing the entire sample, the results showed a correlation between satisfaction of body image and female genitalia. Moreover, when comparing groups with and without dyspareunia, women who experience pain while in a sexual relationship had higher levels of fear and anxiety related to their body image and more negative feelings and beliefs about their genital self-image. A study of women seeking genital aesthetic plastic surgery demonstrated an improvement in both genital image and body image after surgery. The improvement of genital image and body image was observed when the results of the participants were compared, before and within 24 months after the surgery, and after a comparison with a control group. The FGSIS was used to assess genital image, which presented an initial score of approximately 16 points. During the postoperative period, there was an improvement in genital image, and after 24 months it reached a score of approximately 24 points. However, the instrument used to evaluate body image was different from that of the present study[23]. As in the present study, most studies in the literature point to a relation between female body image and genital image.

Although the relation between body image and genital image as described in the present study is in agreement with the results mentioned in the literature, one study reported contradictory findings. Using a population of primiparous and sexually active women, who were on average seven months postpartum. It was observed that the dissatisfaction of body image diminished and that of the genital image increased. In addition, women who underwent vaginal delivery, unlike women who underwent a cesarean section, had higher levels of body satisfaction and a lower genital self-image[24].

More recently, in a total of 69 subacute postpartum women, most participants (97%) had a positive sexual and body appreciation, with the exception of sexual pleasure, where 38% indicated they had less sexual pleasure due to genital alterations[25].Therefore, in order to confirm the relation between female body and genital image, it is necessary to be aware of the different characteristics of the population. Pregnant woman in the postpartum period could experience, in addition to hormonal and psychological influences, physical changes due to pregnancy, affecting the physical perception and the relationship with their own body and/or genitalia, and consequently affecting sexual function.

In the present study, there was a significant correlation between female body and genital image, However, a weak correlation was presented in the statistical analysis[16,19]. Similar results were described in the surveys of DeMaria et al.,[16,19] 2011 and 2012, using the same questionnaire to evaluate genital image. Although studies have described the FGSIS as a reliable tool to evaluate genital image, Herbenick and Reece, [26] suggested that further research was required to understand the suitability of the FGSIS in various populations. With the results of our study, we could form the hypothesis that the FGSIS does not address the dissatisfaction of women with their genital image when dealing with esthetic factors. In Brazil, there has been an exponential increase in the search for genital plastic surgery in recent years (ISAPS, 2014), turning it into one of the most performed surgeries in the country[14]. Another justification for this hypothesis is based on comparisons with body image instruments with body illustrations, whereby the participant is requested to indicate the region of greatest discomfort and/or desire for change[27].

In the present study, 81% of the women were satisfied with their body image, differing from the data in the literature. In a review with studies in Brazilian populations, a dissatisfaction with body image in adults with scores of around 60 to 87% was shown[2]. Another Brazilian study identified a body image dissatisfaction rate of 85.9% for both sexes. When analyzing the characteristics of these women, the majority, approximately 60%, who were dissatisfied with the body, reported excess body weight as their main concern, even though 59% of them were classified as being "within normal range". Moreover, the study also showed that women with a low level of physical activity were those who were most dissatisfied with being overweight[1].

Underlining the findings that a high BMI has a negative influence on body image, the results of this research also showed that women with some level of concern and dissatisfactions with their body were overweight. Overweight women have more negative opinions about the perception of their weight and their bodies, and are more dissatisfied[3,28-32]. In addition to being overweight, women who were dissatisfied with their bodies were the youngest and had a worse genital image. The literature shows that dissatisfaction with body image is similar between young and older women[33-35]. Despite the similarity of satisfaction among women of different ages, younger women are more affected by influences of social imposition and media[33,34].

However, the relationship between being overweight and/or age with genital image is not seen in the literature. It is possible to verify that several genital image studies have been performed in young populations at university, and that this population is satisfied with its genitalia[16,36]. It is believed that there is a possibility that overweight woman and woman unsatisfied with their weight, by neglecting the body, see less of their body and visualize the genitalia to be imperfect. Women who perceive their body as being overweight may have the same perception of their genitalia, and as a consequence have a justification for being dissatisfied. However, in the present study, women over 60 years were not approached for possible comparisons and the age of the women who participated in the research represented a young adult population. In this way, it is not possible to derive the relationship between body and genital image and age.

In the literature, the context of body image is addressed more often than female genital image. However, like body image, genital image is well studied in university populations[2,7,16,37], and these studies barely evaluate the existence of the correlation between the body and vulva[7,16]. Therefore, we consider it important to study whether concerns about the body also extend to the vagina, in environments with populations with heterogeneous characteristics, and across different levels of schooling, and socio-cultural influences, even though the majority of the literature describes body image and genital image in university students. In the present study, a common demographic characteristic was that most participants completed a form of higher education, producing a similarity in the results. The similarity of body and genital image satisfaction of the present study and in the literature implies that more than the educational level of the individual, the culture and society in which one lives can influence the perception of a woman about herself. The justification of this hypothesis is based on the comparison between the financial conditions of the countries where the research was conducted. Most university studies were performed in countries with greater investment in education and culture. The present study, however, deals with women residing in a developing country.

Through questionnaires or photographs of vulvas, surveys evaluate the concepts of genitalia being considered normal and ideal, apart from the satisfaction of woman with their genitalia[7,19]. Due to the absence of an instrument to evaluate genital image in the Portuguese language, it is not possible to verify the main predictors associated with genital image. Moreover, the resources of evaluation of genital image recommend measuring the perception of the genitalia as a factor of satisfaction, with the absence of instruments that can quantify the impact of the appearance of the vulva through visual resources. For body image, this is already well established because there are visual instruments that allow women to point to the region that bothers them the most[27]. Most studies evaluate genital image with a sexual function. In this study, a correlation between body image and genital female image was shown, and questions were raised as to whether the perception of genital image interferes more with aspects of health or perception of the body.

Dissatisfaction with genital image reduces the frequency of women presenting to gynecologic offices and the amount of prevention exams[16]. Therefore, due to the correlation of body and genital image, health professional should, before women become dissatisfied with their body, be attentive to the vulva, and with preventive action, guide them to attend gynecologists, thereby minimizing the risk of diseases and injuries. Professionals who work in sexual health should pay attention to how women observe their body to detect dissatisfactions in genitalia. If women show eating behavior disorders due to dissatisfaction, they should be referred to more specialized professionals. Knowledge about body and genital perception may favor the behavior of health professionals in psychology, sexual and nutritional health, and could help in the recognition of possible indicators for the search for physical activity practices and esthetic procedures. Studies that are part of the line of research of this group, seeking to analyze body and genital image in physically active and sedentary women, as well as their relationships with socio-demographic and clinical data, sexual function, and quality of life, are underway. Also, another project is the elaboration of a computational model that helps health professionals in the evaluation of female genital self-image. We suggest that future research may also evaluate the relation of men with their body and external genital organs.

Study Limitations

From the questionnaires used, the FGSIS is not a validated instrument in the Portuguese language and with the criteria of visualization, the authors decided to make a translation because genital self-image is a relevant research topic for the Brazilian population. This limitation was minimized through reliable analysis. However, the analysis of the study refers to the reliability between the answers, but does not provide internal validity. This justifies the need for studies with a formulation of instruments for the Portuguese language because there is an increase of concerns associated with female genitalia.

Conclusion

The dissatisfaction with body image is associated with poorer genital self-image. BMI and age are predictors of female body image perception. It was not possible to find clinical and socio-demographic data predicting female genitalia self-image factors.

Ethics

Ethics Committee Approval: This study was approved by the Research Ethics Committee of the Bahia School of Medicine and Public Health, where it received the following CAAE number: 14425813.9.0000.5544.

Informed Consent: All patients signed the free and informed consent form.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: P.L., Design: P.L., Data Collection or Processing: C.A.B., A.P.P.B., Analysis or Interpretation: C.A.B., Literature Search: R.S.F., B.B., Writing: T.B.S.G.

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Evaluation of serum cathepsin B, D, and L concentrations in women with late-onset preeclampsia

Geç başlangıçlı preeklampside serum kathepsin B, D ve L düzeylerinin değerlendirilmesi

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Abstract

Objective: The aim of the study was to assess serum cathepsin B, D, and L concentrations in women with late-onset preeclampsia.
Materials and Methods: One hundred forty pregnant women were enrolled in the study, of which 100 subjects were preeclamptic and 40 were healthy controls. Serum concentrations of cathepsin B, D, and L were measured and compared between the preeclamptic and control groups.
Results: Cathepsin B and D concentrations were significantly higher in the preeclamptic group compared with the control group. There was no statistically significant difference between the groups in terms of cathepsin L concentrations. Cathepsin B concentrations were significantly higher in women with preeclampsia with severe features compared with those with preeclampsia alone.
Conclusion: Women with late-onset preeclampsia have significantly higher serum cathepsin B and D concentrations than controls. Cathepsin B and D may be promising biomarkers in women with late-onset preeclampsia.
Keywords: Cathepsin B, cathepsin D, cathepsin L, preeclampsia

Öz

Amaç: Bu çalışmanın amacı geç başlangıçlı preeklampside serum kathepsin B, D ve L düzeylerini değerlendirmektir.
Gereç ve Yöntemler: Çalışmaya 100 preeklamptik ve 40 sağlıklı olmak üzere 140 gebe hasta dahil edildi. Kathepsin B, D ve L serum düzeyleri ölçülerek, preeklamptik ve kontrol grupları arasında karşılaştırıldı.
Bulgular: Serum kathepsin B ve D düzeyleri preeklamptik grupta kontrol grubu ile karşılaştırıldığında anlamlı olarak daha yüksek saptandı. Kathepsin L düzeyleri açısından gruplar arasında istatistiksel olarak anlamlı bir fark yoktu. Kathepsin B düzeyleri şiddetli preeklampsi bulguları olan kadınlarda diğer preeklamptik olgularla karşılaştırıldığında istatistiksel olarak anlamlı daha yüksek bulundu.
Sonuç: Geç başlangıçlı preeklampsili kadınlarda serum kathepsin B ve D düzeyleri kontrol ile karşılaştırıldığında anlamlı olarak daha yüksekti. Geç başlangıçlı preeklampside kathepsin B ve D umut verici biyobelirteçler olabilir.
Anahtar Kelimeler: Kathepsin B, kathepsin D, kathepsin L, preeklampsi

Introduction

Cathepsin proteases have been suggested to be involved in a variety of cellular processes such as apoptosis, angiogenesis, cell proliferation, and invasion[1]. The important roles of cathepsins have been implicated in normal and abnormal placentation;[1] however, research on the serum concentrations of cathepsins in preeclampsia is limited.

Preeclampsia is one of the leading causes of maternal-fetal morbidity and mortality, affecting approximately 3-5% of all pregnancies[2]. Determining late-onset preeclampsia, which is more common than the early-onset preeclampsia,[2] and identification of high risk individuals may be helpful for close monitoring and to minimize adverse outcomes in clinical practice. The aim of the study was to assess serum

PRECIS: Cathepsin B and D may be promising biomarkers in women with late-onset preeclampsia.

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cathepsin B, D, and L concentrations in women with late-onset preeclampsia and to determine the impact of cathepsins with regard to the presence of severe features.

Cathepsin B and L are cysteine proteases that have important roles in placental development and in the physiology of normal and pathologic conditions. Cathepsin B is reported to be predominantly located in placental and decidual macrophages, which may be important in mediating villous angiogenesis and decidual apoptosis, and cathepsin L is found to be expressed in invasive cytotrophoblasts[1]. Both cysteine proteases are determined to have critical roles during normal placentation and in the etiology of preeclampsia[1]. Cathepsin D is an aspartic protease that participates in the trophoblast invasion process,[3] and the contribution of cathepsin D is also suggested in the pathogenesis of preeclampsia[4,5].

However, there are a limited number of studies that evaluated serum concentrations of cathepsins in preeclamptic women and the studies had small sample sizes. Additionally, to our knowledge this is the first study to evaluate serum cathepsin B, D, and L concentrations in late-onset preeclampsia.

Materials and Methods

After obtaining written informed consent from all participants, one hundred forty pregnant women were enrolled in the study, of which 100 subjects were preeclamptic (late-onset preeclampsia diagnosed at ≥34 weeks gestation) and 40 were healthy controls. The study protocol was approved by the Marmara University Ethics Committee (approval number: 09.2017/411).

Preeclampsia and severe features were defined according to current recommendations based on the 2013 American College of Obstetricians and Gynecologists' consensus guidelines[6]. The common inclusion criteria for both groups were: singleton pregnancy at ≥34 weeks gestation, normal fetal morphology, non-smoking, and the absence of concomitant disease.

Serum concentrations of cathepsin B, D, and L were measured using an enzyme-linked immunosorbent assay (ELISA) by using the human cathepsin B, D, (Elabscience, Houston, TX) and L (Invitrogen, Carlsbad, CA) ELISA kits according to the manufacturer's instructions and then compared between the preeclamptic and control groups.

Statistical Analysis

All data were analyzed using the Statistical Package for the Social Sciences 20.0 for Windows program (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). The distribution of data was measured using the Kolmogorov-Smirnov test. Data are presented as mean ± standard deviation or n (%). Student's t-test was used for comparisons of means, and the chi-square test was used to compare categorical variables between the two groups, as appropriate. Pearson's correlation test was used for the correlation analyses. The receiver operating characteristics (ROC) curve of cathepsin B in predicting severe preeclampsia was analyzed. The results were considered significant if p values were <0.05, and highly significant if p<0.01.

Results

One hundred forty pregnant women were enrolled in the study, of which 100 subjects were preeclamptic (late-onset preeclampsia diagnosed at ≥34 weeks' gestation) and 40 were healthy controls. Twenty-six subjects in the preeclamptic group had severe features.

Cathepsin B concentrations were significantly higher in the preeclamptic group compared with the control group (4.24±3.51 ng/mL vs. 2.04±1.97 ng/mL, respectively; p<0.001). Cathepsin D concentrations were significantly higher in the preeclamptic group compared with the control group (4.97±1.24 ng/mL vs. 4.20±1.65 ng/mL, respectively; p<0.01). There was no statistically significant difference between the groups in terms of cathepsin L concentrations (Table 1).

There were no statistically significant differences between the groups in terms of age, body mass index, and gestational age. Systolic and diastolic blood pressures and serum uric acid concentrations were significantly higher in the preeclamptic group (Table 1). The mean value for 24-hour urine protein in the preeclamptic group was 2980.12±2516.33 mg/24 h. Cathepsin B concentrations were found to be positively

Table 1. Clinical and biochemical characteristics of the groups

	Preeclampsia n=100	Control n=40	p
Age (years)	29.93±6.03	28±6.60	0.099
Gestational age (weeks)	36.52±1.89	37.12±1.45	0.072
BMI (kg/m²)	31.42±4.51	30.13±4.06	0.118
Nulliparous n (%)	52 (52)	23 (57.5)	0.556
Systolic blood pressure (mm/Hg)	153.27±14.41	117.97±12.20	<0.001[a]
Diastolic blood pressure (mm/Hg)	97.38±10.03	72.80±10.40	<0.001[a]
Uric acid (mg/dL)	5.62±1.56	4.60±1.15	<0.001[a]
Cathepsin B (ng/mL)	4.24±3.51	2.04±1.97	<0.001[a]
Cathepsin D (ng/mL)	4.97±1.24	4.20±1.65	0.003[a]
Cathepsin L (ng/mL)	2.54 ±1.38	2.19±0.73	0.131

Values are expressed as mean ± standard deviation or n (%), BMI: Body mass index
[a]p<0.01.

correlated with uric acid concentrations (r=0.343, p<0.01) in women with preeclampsia. Cathepsin B concentrations were significantly higher in women with preeclampsia with severe features (n=26) compared with those with preeclampsia alone (6.89±3.51 ng/mL vs. 3.31±3.02 ng/mL, respectively; p<0.001). The ROC curve of cathepsin B in predicting severe preeclampsia was analyzed. The area under the curve of cathepsin B was 0.81 (95% CI: 0.71-0.90) and the optimal cut-off level was 4.71 ng/mL, yielding 85% sensitivity and 74% specificity.

Discussion

Preeclampsia is a multifactorial clinical state that adversely affects several vital organs and increases the morbidity and mortality of both the fetus and the mother[7-9]. Although there is growing evidence and there are many theories addressing its heterogeneous nature, the pathogenesis is not yet fully understood[7-9].

The aim of the study was to evaluate cathepsin concentrations in women with late-onset preeclampsia and to determine the impact of cathepsins with regard to the presence of severe features. To our knowledge, this is the first study to emphasize the importance of cathepsin B, D, and L serum concentrations in women with late-onset preeclampsia.

In our study, we found significantly higher serum concentrations of cathepsin B and D in the preeclamptic group compared with the control group; however, cathepsin L concentrations were similar between the two groups. Moreover, cathepsin B concentrations were found to be positively correlated with uric acid concentrations in women with preeclampsia. Our data also indicate that cathepsin B concentrations were significantly higher in women with preeclampsia with severe features compared with those with preeclampsia alone, emphasizing the importance of cathepsin B in women with preeclampsia and in the subgroup of preeclamptic women with severe features.

Cysteine cathepsins are lysosomal peptidases that comprise cathepsin B and cathepsin L, which have many physiologic roles in different organs and tissues including cancer progression, tumor proliferation triggers, invasion, and metastasis,[10,11] and it has been demonstrated that abnormal concentrations and activities may correlate with various physiologic processes and human diseases, such as neurodegenerative disorders,[12] regulation of apoptosis, immune responses, inflammatory diseases,[13] cancer,[11,14,15] psoriasis,[16] and cardiovascular[17,18] and kidney diseases[19].

In a study evaluating serum concentrations of cathepsin B and L that included 40 women with preeclampsia and 38 women as controls, higher concentrations of cathepsin B and L were reported in women with preeclampsia; however, no statistically significant difference was reported between women with severe preeclampsia compared with subjects with mild preeclampsia[20]. The distribution and abnormal expression concentrations of cysteine cathepsins were also reported in preeclamptic placentas indicating their important roles during normal placentation and in the etiology of preeclampsia[1].

Circulating concentrations of cathepsin B and D were determined in a cohort of 72 pregnant women in which 25 were preeclamptic and 47 were normotensive. In accordance with our study, cathepsin B concentrations were found to be significantly increased in preeclamptic women, whereas in contrast to our data, no significant difference was found in cathepsin D concentrations between the preeclamptic and control groups, and no correlation was found between the cathepsin concentrations and the severity of preeclampsia[21]. The differential expression or aberrant release of cathepsin proteases from trophoblasts or other types of cells were suggested to have a key role in the pathophysiology of preeclampsia[21].

Cathepsin D is a lysosomal aspartic proteinase that plays a key role in protein degradation and in apoptotic processes that are induced by oxidative stress, cytokines, and aging[22]. Few studies have evaluated the impact of cathepsin D in women with preeclampsia. In a study evaluating cathepsin D activity in the umbilical cord, it was reported that preeclampsia was associated with a reduction in the activity of cathepsin D in human umbilical cord[5]. The placentas of preeclamptic subjects were also evaluated by Kim et al.,[23] and an overexpression of cathepsin D in the placentas from preeclamptic patients was demonstrated suggesting a trigger of apoptosis. In another study, circulating serum concentrations of cathepsin D were found to be significantly lower in the preeclamptic group (n=15) than in normotensive pregnancies (n=35) and also similar to those in non-pregnant healthy patients (n=20); however, a limited number of preeclamptic cases were included in the study and further studies with larger sample sizes were suggested[4]. In our study, we found that serum cathepsin D concentrations were significantly higher in the preeclamptic group compared with the control group.

Study Limitations

The limitation of the study is its small sample size. Further studies with larger sample sizes are needed.

Conclusion

This is the first study to demonstrate the impact of cathepsin B, D, and L on late-onset preeclampsia. There are few previously published studies with small sample sizes that have reported conflicting results about the importance of cathepsins in the pathogenesis of preeclampsia. The present study shows that women with late-onset preeclampsia have significantly higher serum cathepsin B and D concentrations than controls, and cathepsin B concentrations are even higher in the subgroup of preeclampsia that has severe features. In summary, the study

suggests that cathepsin B and D may be promising biomarkers in women with late-onset preeclampsia. Moreover, cathepsin B may be useful in early identification of preeclamptic women with severe features.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of the Marmara University (approval number: 09.2017/411).
Informed Consent: Consent form was filled out by all participants.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.Y., G.A.İ., Concept: B.Y., G.A.İ., Design: B.Y., G.A.İ., Data Collection or Processing: B.Y., G.A.İ, Analysis or Interpretation: G.A.İ., Literature Search: B.Y., G.A.İ., Writing: G.A.İ.
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Comparison of hepatitis B, hepatitis C, and HIV seropositivity of Syrian and Turkish pregnant women

Suriyeli ve Türk gebelerin hepatit B, hepatit C ve HIV seropozitifliklerinin karşılaştırılması

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Abstract

Objective: In this study, we aimed to compare the seroprevalence of hepatitis B (HBV), hepatitis C (HCV), and human immunodeficieney viruse (HIV) in Syrian pregnant women and Turkish pregnant women in our hospital.

Materials and Methods: In our study, a total of 68,169 Turkish pregnant women who received HB surface antigen (HBsAg), HB surface antibody (anti-HBs), HCV antibody (anti-HCV), anti-HIV test, and a total of 11,015 Syrian pregnant patients who received HBsAg, anti-HBs, anti-HCV and anti-HIV tests were examined retrospectively between January 2012 and January-2018 in Universty of Health Sciences Kanuni Sultan Süleyman Training and Research Hospital, Obstetrics and Gynecology Clinic.

Results: In our study, the rates of HBsAg, anti-HCV, and anti-HIV seropositivity were 1.1%, 0.1%, and 0.03% in Syrian pregnant women between 2012 and 2018, respectively. In the other study group, in Turkish pregnant women, HBsAg, anti-HCV, and anti-HIV seropositivity rates for 2012 and 2018 were found as 1.8%, 0.2%, and 0.08%, respectively.

Conclusion: Although there were no significant differences between the HBsAg, anti-HCV, and anti-HIV results of both groups, the anti-HBs positivity was higher at a significant level in Turkish pregnant women. The reason of the significantly higher anti-HBs positivity levels in pregnant women might stem from the fact that women are vaccinated and controlled regularly due to the policies in this regard in our country.

Keywords: Hepatitis B, hepatitis C, HIV, pregnancy, seroprevalence

Öz

Amaç: Bu çalışmada hastanemizdeki Suriyeli mülteci gebelerdeki hepatit B (HBV), hepatit C (HCV) ve insan immün yetmezlik virüsü (HIV) seroprevalansının Türk gebeler ile karşılaştırılması amaçlanmıştır.

Gereç ve Yöntemler: Çalışmamızda Ocak-2012 ve Ocak-2018 yıllarında Sağlık Bilimleri Üniversitesi Kanuni Sultan Süleyman Eğitim ve Araştırma Hastanesi Kadın Hastalıkları ve Doğum Kliniği'nde HB yüzey antijeni (HBsAg), HB yüzey antikoru (anti-HBs), HC antikoru (anti-HCV), anti-HIV testi yapılan toplam 68,169 Türk gebe ve HBsAg, anti-HBs, anti-HCV ve anti-HIV testi yapılan toplam 11,015 Suriyeli gebe hasta retrospektif olarak incelenmiştir.

Bulgular: Çalışmamızda 2012 ve 2018 yıllarında Suriyeli gebelerde HBsAg, anti-HCV, anti-HIV seropozitiflik oranları sırasıyla %1,1, % 0,1 ve %0,03 olarak saptandı. Diğer çalışma grubu olan Türk gebelerde ise 2012 ve 2018 yılları için HBsAg, anti-HCV ve anti-HIV seropozitiflik oranları sırasıyla %1,8, %0,2 ve %0,08 olarak tespit edildi.

Sonuç: Her iki grup arasında HBsAg, anti-HCV ve anti-HIV sonuçları arasında anlamlı fark izlenmezken, anti-HBs pozitifliği Türk gebelerde anlamlı olarak daha fazla bulunmuştur. Gebelerde anti-HBs pozitifliğinin anlamlı olarak fazla bulunmasının nedeni ülkemizdeki aşılama politikalarının düzenli ve kontrollü olmasından kaynaklanıyor olabilir.

Anahtar Kelimeler: Hepatit B, hepatit C, HIV, gebelik, seroprevelans

PRECIS: This study was conducted to compare the seroprevalence of hepatitis B, Hepatitis C, and HIV in Syrian pregnant women and Turkish pregnant women.

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Introduction

Infection is one of the most important factors increasing perinatal morbidity and mortality. Studies have shown that infections that present during the gestational period have the risk of infecting the fetus by exceeding the placenta and increase fetal mortality and morbidity[1].

Since 2011, because of the civil war, about 2.5 million Syrian people have been forced to abandon their countries and live in refugee camps in neighboring countries. Syrians have been provided with temporary protection by Turkey and are the densest group of asylum seekers in our country. Approximately 2.7 million Syrian refugees have already been distributed in Turkey, which has world's largest population of Syrian refugees[2]. Refugees may face housing, food, medical accessibility, and language barriers when they come to temporary or new host countries. The Turkish Government has provided free healthcare for Syrian refugees, and the facilities to health services has been increased.

The rates of pregnancy and birth are high in Syrian refugees in our country[3]. Due to limited opportunities in communication, healthcare workers are also affected and difficulties are experienced in health services. For these reasons, adequate measures against infectious diseases cannot be taken and the mother, fetus, and health workers are at risk. The failure of Syrian pregnant women to adapt to Turkish screening and vaccination programs, and most Syrian pregnant women being seen by physicians during the first birth is a common problem.

This study was conducted to compare the hepatitis B virus (HBV), hepatitis C virus (HCV), and human immmunodeficiency virus (HIV) seropositivity of Turkish pregnant women and that of Syrian migrant pregnant women who gave birth in our hospital.

Materials and Methods

Our study was performed retrospectively after approval was obtained from the Local Ethics Committee of University of Health Sciences Kanuni Sultan Suleyman Training and Research Hospital (approval number: 2018.10.36). A total of 11,015 Syrian pregnant women and 68,169 Turkish pregnant women who presented due to pregnancy and who gave birth were included in the study. The women presented to University of Health Sciences Kanuni Sultan Süleyman Training and Research Hospital, Clinic of Obstetrics and Gynecology of İstanbul University of Health Sciences between 2012 and 2018. Patients' files were retrospectively scanned and their ages and ethnicity (Syrian refugee-Turkish population) were recorded. Venous blood samples from all patients were tested for HBsAg, anti-HBs, anti-HCV and anti-HIV using the micro-ELISA method. Suspected positive anti-HIV sera samples were confirmed using the western blot method.

Statistical Analysis

The Statistical Program for the Social Sciences (SPSS Chicago, IL, USA) program was used to evaluate all collected data. Continuous variables with normal distribution were reported as the average. P values less than 0.05 were considered statistically significant.

Results

In the study, 11,015 Syrian immigrant pregnant women and 68,169 Turkish pregnant women were compared in terms of serology. The serology results of the study and control groups are given in Table 1. A total of 68,169 Turkish patients who gave birth in our hospital and 11.015 Syrian patients were examined for HBsAg, 67,760 Turkish and 11,004 Syrian pregnant for anti-HCV, 67,871 Turkish and 11,015 Syrian pregnant women for anti-HIV, and 7130 Turkish and 180 Syrian pregnant women for anti-HBs. The average age of the Turkish women (28±6 years) was significantly higher than that of the Syrian migrant women (25±6.02 years) ($p<0.001$). Anti-HCV was positive in 0.2% of 67,760 Turkish pregnant women and 0.1% of 11,004 Syrian pregnant women. There was no statistically significant difference between anti-HCV positivity of either group.

Anti-HIV was positive in 57 of 68,169 Turkish pregnant women, 12 of these patients were confirmed and seen as negative in our records. The other patients' verification results could not be obtained. Anti-HIV was positive in 4 cases of

Table 1. Comparison of serology results of Turkish and Syrian immigrant pregnant women

	Turkish pregnant women n (%)			Syrian pregnant women n (%)			p**
	Positive	Negative	Total	Positive	Negative	Total	
Anti-HCV	200 (0.2%)	67,560 (99.7%)	67,760	15 (0.1%)	10,989 (99.8%)	11,004	0.241
Anti-HIV	57* (0.08%)	67,814 (99.9%)	67,871	4 (0.03%)	11,011 (99.9%)	11,015	0.232
HBsAg	1257 (1.8%)	66,912 (98.1%)	68,169	127 (1.1%)	10,888 (98.8%)	11,015	0.230
Anti-HBs	1487 (26.3%)	5643 (79.1%)	7130	20 (11%)	160 (88.8%)	180	0.001

*Only 12 out of 57 HIV positive patients were verified

**p values were calculated between positive groups and significance was accepted as $p<0.05$, HCV: Hepatitis C virus, HIV: Human immmunodeficiency virus, HBsAg: Hepatitis B surface antigen, Anti-HBS: Anti hepatitis B surfage antigen

11,015 Syrian pregnant women, and four of our patients were found to be negative in our records of verification.

When HBsAg positivity of both groups was examined, HBsAg was studied in all pregnant women who gave birth in our hospital. HBsAg positivity was found in 1.8% of the 68,169 Turkish pregnant women and in 1.1% of the 11,015 Syrian pregnant women.

Although the total number of patients studied for anti-HBs was less than the others, 26.3% of 7130 patients with anti-HBs in Turkish pregnant women were positive, and in Syrian patients, only 180 patients were examined and 11% of them were positive. When these two groups were compared with each other, anti-HB outcomes were significantly higher in Turkish patients.

Syrian pregnant women were divided into two groups, as those who were under and over the age 35 years. When the serologic results were compared between the two groups, both anti-HCV and HBsAg were found as significantly higher for patients over the age of 35 years ($p<0.001$ and $p=0.002$, respectively). There was no statistically significant difference of anti-HIV and anti-HB positivity between the two groups. The serologic results of these groups are given in Table 2.

Discussion

Since 2011, Syrians have migrated to many countries due to the Syrian civil war between rebels and government forces. The majority of the refugees have chosen to be refugees in Turkey. According to the April 2016 United Nations Refugee Agency data, there were 2,749,140 registered Syrian refugees in Turkey[2]. The increasing number of uncontrolled and informal Syrian refugees causes many social and health problems. It is important to know the hepatitis and HIV prevalence in both the refugee and the local community.

There is no congenital anomaly or teratogenic effect of HBV and it does not pass through the placenta[4]. When the case of infection from the mother to the infant is considered, it may be due to contact with various maternal fluids during or after childbirth or in the vagina during vaginal delivery, or by swallowing mother's blood or after a placental injury[5]. HBsAg has been shown in the mother's milk, and theoretically, it can be considered as a breast milk infectious agent; however, infectiousness is decreased by 85-95% with the newborn vaccination program, which is routine in our country[6].

HBV infection is an important health problem in our country as it is in developing countries. In recent years, the screening of donors for hepatitis infection, progress in the sterilization of instruments used in healthcare, and the increase of disposable materials has reduced the infectivity of the infection to a relatively small extent. In addition, HBV vaccination has been routinely practiced in our country since 1998 at the 0 years age group. Considering that HBV vaccine administered in newborns and immunoglobulins significantly prevent vertical passage, it shows us how important it is for pregnant women to be screened for HBsAg.

HCV infection may also pass vertically through the newborn. Babies of high-viral-loaded mothers are at greater risk. However, this ratio is lower than that of HBV[7]. It has been observed that most HIV infections are seen in childhood in the perinatal period and this transition is between 13-43%. It is known that infants of pregnant women who are known to be HIV-positive and who are treated with zidovudine during their pregnancies have a 25% reduction in the risk of transmission from mother to infant with ongoing postpartum 6-week zidovudine treatment[8].

There are many studies in the literature showing the maternal outcomes of refugees from different ethnic groups, but there are few studies comparing HBV, HCV, and HIV infections of the Syrian population in Turkey. In the study conducted by İnci et al.,[9] on 4186 pregnant women including 2158 Syrians and 2028 Turks, the rate of vaccination of pregnant women was investigated, and the HBsAg positivity rates before and after vaccination were analyzed. HBsAg positivity was 1.4% among all pregnancies, which was 1.8% among Turkish women and 1.1% among Syrian women.

In the study of Çift et al.,[10] comprising 297 Syrian refugees and 300 Turkish women, a total of 597 participants who presented due to pregnancy and giving birth, the anti-HBs

Table 2. The analysis of Syrian pregnant women based on age

	Syrian pregnant women aged under 35 years n (%)			Syrian pregnant women aged over 35 years n (%)			p*
	Positive	Negative	Total	Positive	Negative	Total	
Anti-HCV	10 (0.1%)	10,083 (99.9%)	10,093	5 (0.5%)	906 (99.5%)	911	<0.001
Anti-HIV	4 (0.0%)	10,104 (100%)	10,108	0 (0.0%)	905 (100%)	905	0.549
HBsAg	107 (1.1%)	10,001 (98.9%)	10,108	20 (2.2%)	885 (97.8%)	905	0.002
Anti-HBs	18 (10.8%)	148 (89.2%)	166	2 (14.3%)	12 (85.7%)	14	0.694

*p values were calculated between positive groups and significance was accepted as $p<0.05$, HCV: Hepatitis C virus, HIV: Human immmunodeficiency virus, HBsAg: Hepatitis B surface antigen

immunoglobulin G (IgG) positivity ratio in Turkey (13.9%) was found to be statistically higher than in Syria (8.5%). Again, in this study, the rates of HBsAg and anti-HCV in Syrian pregnancies were found as 0.3%, and they were 0.8% and 0%, respectively, in Turkish pregnant women. In our study, HBsAg and anti-HCV positivity were found as 1.8% and 0.2% in Turkish women and 1.1% and 0.1% in Syrian pregnant women, respectively. However, the difference between this study and our study is that there were no anti-HBs IgG and IgM data of the patients.

In the study conducted by Madendag et al., [11] which only investigated Turkish pregnant women, 1,910 HBsAg positivity of 90.351 pregnancies (2.11%), anti-HCV positivity in 102 of 60,729 pregnant women (0.17%), and anti-HIV positivity was detected in 3 of 60,562 pregnancies (0.004%).

In a study conducted by Coppola et al.[12] on HBV infection on 1212 immigrants in Italy, they found HBsAg positivity in 116 patients (9.6%). A total of 606 (50%) patients had negative HBsAg/anti-HB antibody values. It has been reported that immigrants have to undergo HBV vaccination after 4.5 years of living in Italy because immigrants' serology has not been assessed, no vaccination has been performed, and immunization has not been provided so far.

Considering the number of Syrian pregnancies in our country and a group of patients who were not previously on the screening program, HBV, HCV, and HIV screening of patients

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Increased nuchal translucency and pregnancy outcomes: experience of Başkent University Ankara Hospital

Artmış ense saydamlığı ve gebelik sonuçları: Başkent Üniversitesi Ankara Hastanesi deneyimi

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Abstract

Objective: First trimester nuchal translucency (NT) measurement is considered to be an important tool in antenatal follow-up. This study aimed to evaluate the outcomes of pregnancies with increased NT at Başkent University Ankara Hospital between 2004 and 2016.

Materials and Methods: Patients with NT measurements ≥1.5 multiples of median (MoM) were divided into two groups; group I included increased NT cases without fetal anomalies (either abnormal fetal karyotype or congenital structural anomalies) or loss (intrauterine fetal death), and group II included increased NT cases with fetal anomalies or loss. The groups were compared with each other with respect to maternal demographic features and NT measurements.

Results: Karyotype analyses were normal in 73.1% of cases with increased NT (57/78). Among those, 21.1% (12/57) had structural anomalies, and to specify, 9.6% (5/52 over 18 weeks) had cardiac anomalies. Although maternal demographic features did not differ significantly, NT measurements, both as millimeters and MoM, were significantly higher in group II ($p<0.05$). According to the receiver operating characteristic (ROC) curves, the optimal cut-off values for NT measurements for predicting fetal anomalies or loss were 3.05 mm and 2.02 MoM. NT measurement >7 millimeters or NT MoM >4.27 resulted in poor fetal outcomes without exception.

Conclusion: Higher NT measurements indicate poorer pregnancy outcomes. Our study indicates that fetal echocardiography must be considered for all cases with increased NT.

Keywords: Nuchal translucency, abnormal karyotype, cardiac anomaly

Öz

Amaç: Birinci trimester ense saydamlığı (NT) ölçümü antenatal takipte önemli bir araç olarak kabul edilmektedir. Bu çalışmada Başkent Üniversitesi Ankara Hastanesi'nde 2004-2016 yılları arasındaki artmış NT'si olan gebeliklerin sonuçlarını değerlendirmeyi amaçladık.

Gereç ve Yöntemler: NT ölçümleri ≥1,5 MoM olan olgular iki gruba ayrıldı. Grup I artmış NT'ye fetal anomalilerin (anormal fetal karyotip, konjenital yapısal anomaliler) veya kaybın (intrauterin fetal ölüm) eşlik etmediği olguları içerirken; grup II artmış NT'ye fetal anomalilerin veya kaybın eşlik ettiği olguları içerdi ve gruplar maternal demografik özellikleri ve NT ölçümlerine göre birbirleri ile karşılaştırıldı.

Bulgular: NT artışı olan olguların %73,1'inde karyotip analizleri normaldi (57/78). Bunların arasında, %21,1'inde yapısal anomaliler vardı ve %9,6'sında (18 hafta üzeri 5/52) kardiyak anomalilerin olduğu belirlendi. Maternal demografik özellikler önemli ölçüde farklılık göstermemesine rağmen, NT ölçümleri hem milimetre hem de MoM değerleri olarak grup II'de anlamlı derecede daha yüksekti (n=35) ($p<0,05$). ROC eğrilerine göre fetal anomalilerin ve kaybın

PRECIS: First trimester nuchal translucency measurement is an important tool to recognize genetic abnormalities and many structural anomalies.

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öngörülmesinde NT ölçümleri için uygun sınır değerler 3,05 mm ve 2,02 MoM idi. NT ölçümü >7 mm veya NT MoM >4,27 istisnasız kötü fetal sonuçlarla sonuçlandı.
Sonuç: Daha yüksek NT ölçümleri daha olumsuz gebelik sonuçlarına işaret eder. Bizim çalışmamız fetal ekokardiyografinin NT artışı olan tüm olgular için düşünülmesi gerektiğini gösterdi.
Anahtar Kelimeler: Ense saydamlığı, anormal karyotip, kardiyak anomali

Introduction

Nuchal translucency (NT) is the sonographic visualization of subcutaneous fluid accumulation behind the fetal neck in the first trimester. Ultrasonographic NT measurement at 11-13^6 gestational weeks of pregnancy was introduced into clinical practice in the 1990s as a new method of aneuploidy screening, combined with maternal age and serum biochemical markers[1]. NT is supposed to be increased when it is ≥95th percentile or ≥1.5 multiples of median (MoM) for a certain crown-rump length (CRL) measurement. Although the definitions may vary in the literature, any value ≥3.5 mm is ≥99th percentile for any gestational age between 11-13^6 weeks and considered to be absolutely abnormal, requiring fetal karyotyping as well as detailed anatomic examination with fetal echocardiography in the second trimester.

NT was primarily regarded as a marker of trisomies 21, 18, and 13, and Turner syndrome; however, increasing evidence suggests that abnormal NT measurements might also be related to other chromosomal abnormalities and genetic syndromes, structural anomalies, skeletal dysplasia, congenital infections, metabolic and hematologic disorders and other rare conditions[2]. The proposed mechanisms underlying increased NT, whether septated or not, are cardiac dysfunction, abnormal lymphatic drainage, venous congestion in the head and neck, altered composition of the extracellular matrix, fetal anemia, fetal hypoproteinemia, and fetal infection[3]. Increased NT may also be associated with generalized fetal hydrops[4].

The aim of this study was to evaluate the outcomes of pregnancies with increased NT detected at 11-13^6 gestational weeks at Başkent University Ankara Hospital from 2004 to 2016. We also aimed to consider these results in association with previous evidence to improve counseling for patients with increased NT.

Materials and Methods

This study was approved by the Institutional Review Board and Ethics Committee of Başkent University (approval no: KA09/296). We reviewed the perinatology records of Başkent University Ankara Hospital from 2004 to 2016 to identify pregnancies with increased NT. Patients' files were reviewed to determine maternal demographic features, results of karyotype analysis, incidence and types of fetal anomalies, and pregnancy outcomes. Cases without karyotype analyses were excluded.

NT measurement was performed as originally described by the Fetal Medicine Foundation[1]. The NT measurement in millimeters was converted to MoM according to the CRL, using the NT calculator program of the Fetal Medicine Foundation. Any value ≥1.5 MoM was defined as increased NT. Maternal serum antibody screening was performed for congenital infections including toxoplasma, cytomegalovirus, rubella, and parvovirus B19. Fetal anomaly scanning was performed after the 18th gestational week.

Study cases were categorized in two groups after excluding cases with unknown pregnancy outcomes: group I included cases of increased NT without fetal anomalies (either abnormal fetal karyotype or congenital structural anomalies) or loss (intrauterine fetal death), and group II included increased cases of NT with fetal anomalies or loss. The two groups were compared with respect to maternal age, gravidity, parity, CRL at the time of NT measurement, and NT measurements.

Statistical Analysis

Statistical analysis were performed using Student's t-tests or the Mann-Whitney U test where appropriate, using the SPSS program. The results were considered to be statistically significant at $p<0.05$. The rates of preterm delivery, small for gestational age (SGA) and large for gestational age (LGA) newborns in group I were calculated. Preterm delivery was accepted as deliveries before 37 gestational weeks. SGA was defined as birth weight below the 10th percentile, and LGA was defined as birth weight above the 90th percentile.

The receiver operating characteristic (ROC) curve for NT measurements was drawn using SPSS to determine the optimal cut-off values for discriminating between groups I and II.

Results

A total of 94 pregnant women underwent invasive diagnostic procedures because of increased NT from 2004 to 2016. Maternal serum screening for congenital infections was negative in all cases. Out of the 94 women, 78 with known pregnancy outcomes were included in the study. Among these 78 pregnancies, 74 were singletons (94.9%), 3 were twin pregnancies, and 1 was a triplet pregnancy. Selective fetocide was performed in 2 of the multiple pregnancies for a hydropic co-twin with trisomy 21 and a co-triplet with structural anomalies, respectively

The mean maternal age of the study group (n=78) was 31.5±6.05 (range, 20-47) years. The mean gravidity was 1.82±1.21 (range, 1-6), the mean parity was 0.45±0.69 (range,

0-3), the mean NT measurements were 2.62±1.31 (range, 1.5-6.76) MoM, and 3.93±2.0 (range, 2-10) mm. Among the 78 pregnancies, 34 (43.6%) had NT measurements ≥3.5 mm. Karyotype analyses were reported to be abnormal in 21 (26.9%) and normal in 57 (73.1%) of the 78 cases of increased NT. Among the entire study group, 50 (64.1%) pregnancies resulted in live births, 22 (28.2%) were terminated, selective fetocide was performed in 2 (2.6%), and intrauterine exitus occurred in 4 (5.1%). Abnormal karyotype results were present in 2 live births, 17 terminations, 1 selective fetocide, and 1 intrauterine exitus case. Structural defects with normal karyotype results were present in 5 live births, 5 terminations, 1 selective fetocide, and 1 intrauterine exitus case (Figure 1) (Table 1).

There were 43 cases of increased NT without fetal anomalies or loss (group I) and 35 increased NT cases with fetal anomalies or loss (group II). Group II comprised 21 (26.9%) cases with abnormal karyotype results: trisomy 21 in 9 (11.5%), trisomy 18 in 4 (5.1%), Turner syndrome in 6 (7.7%), deletion of 7q in 1 (1.3%), and duplication of 4p in 1 (1.3%). Twelve (15.3%) patients in group II had fetal structural anomalies despite normal karyotype: seven cases had multiple anomalies including 2 with cardiac anomalies, 3 had isolated cardiac anomalies, 1 had cleft lip and palate, and 1 had uretero-pelvic stenosis. Of the 52 pregnancies with normal karyotypes that continued beyond 18 weeks of gestation, cardiac anomalies were detected in 5 cases (9.6%), including aortic coarctation, complex cardiac anomalies, and ventricular septal defects in 1, 2, and 2 fetuses, respectively. One of these 5 fetuses had an NT measurement <3.5 mm (2.4 mm). Intrauterine exitus with no detected abnormality was observed in 2 pregnancies (Table 1). There was no significant difference in maternal age, gravidity, parity, or CRL at the time of NT measurement between groups I and II. However, NT measurements, both as millimeters and MoM, were significantly higher in group II ($p<0.05$) (Table 2). According to the ROC curves, the optimal cut-off values for NT measurements for predicting fetal anomalies or loss were 3.05 mm and 2.02 MoM (Figure 2). In our study population, all cases with NT measurements >7 mm or NT MoM >4.27 were associated with fetal anomalies or loss.

The rates of preterm birth, SGA and LGA newborns in the increased NT group without fetal anomalies or loss (group I) were 13.9%, 13.9%, and 4.7%, respectively. Pregnancy outcomes in cases of increased NT and normal karyotype can be observed in Table 1. Perinatal outcomes of the all study participants are summarized in Figure 3.

Discussion

The measurement of fetal NT between 11 and 13^6 weeks of gestation is used as a screening method for chromosomal

Table 1. Pregnancy outcomes in cases with increased NT and normal karyotype

	Increased NT and normal karyotype with congenital anomalies		Increased NT and normal karyotype with no congenital anomalies		
Increased NT and normal karyotype n=57	n=12	Multiple anomalies (5) Cardiac + multiple anomalies (2) Isolated cardiac anomalies (3) Cleft lip and palate (1) Ureteropelvic stenosis (1)	n=45		**Total**
Terminations (5) or selective fetocide (1) n=6	6 (50%)		0 (0%)		6 (10.5%)
IU ex n=3	1 (8.3%)		2 (4.4%)		3 (5.3%)
Live births n=48	5 (41.7%)		43 (95.6%) SGA (6, 13.9%) LGA (2, 4.7%)	Preterm birth (6, 13.9%)	48 (84.2%)
Total	**12 (21.1%)**		**45 (78.9%)**		**57**

NT: Nuchal translucency, SGA: Small for gestational age, LGA: Large for gestational age

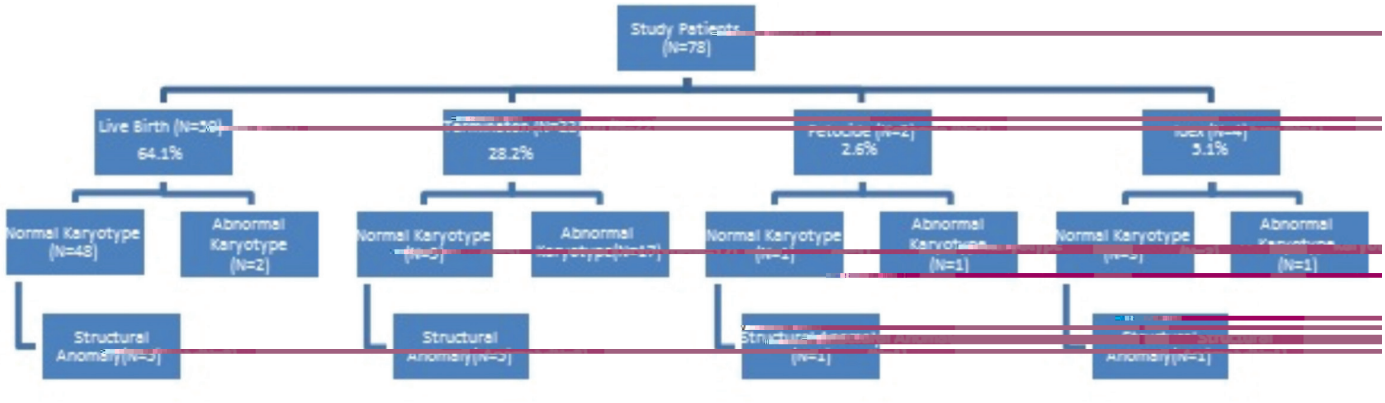

Figure 1. Fetal outcomes in cases undergoing invasive diagnostic procedures because of increased first-trimester nuchal translucency

Table 2. Demographic features, crown-rump length, and nuchal translucency in two increased NT groups without and with fetal anomalies or loss

	Group I NT increase without fetal anomalies or loss n=43				Group II NT increase with fetal anomalies or loss n=35				
	Mean	SD	Minimum	Maximum	Mean	SD	Minimum	Maximum	p
Maternal age (years)	31.56	5.92	20.00	47.00	31.43	6.30	20.00	47.00	0.926
Gravidity	1.74	1.11	1.00	6.00	1.91	1.33	1.00	6.00	0.710
Parity	0.42	0.58	0.00	2.00	0.49	0.81	0.00	3.00	0.924
CRL (mm)	57.40	7.99	45.00	76.00	58.21	10.37	45.00	84.00	0.698
NT (mm)	3.10	1.24	2.00	7.00	4.96	2.27	2.20	10.00	0.001
NT MoM	2.07	0.72	1.50	4.26	3.30	1.54	1.50	6.76	0.001

CRL: Crown-rump length, NT: Nuchal translucency, SD: Standard deviation, MoM: Multiples of median

abnormalities in general practice. In fact, besides chromosomal abnormalities, increased NT may be due to several other problems[2]. Higher NT measurements indicate poorer outcomes and are usually associated with chromosomal defects and structural anomalies[5-7].

Pan et al.,[8] detected chromosomal abnormalities using quantitative fluorescence polymerase chain reaction in 53 of 175 cases (30.2%), with a cut-off value for NT of ≥3.5 mm (99th percentile for 11-13^{6} gestational weeks). In their study, 20 cases (17.5%) had structural defects with normal karyotypes. Lithner et al.,[9] observed abnormal karyotypes in 164 of 341 cases with increased NT (48%), whereas 12 of 139 cases with normal karyotypes had structural anomalies (8.6%). In our study, the cut-off value for NT was ≥1.5 MoM; abnormal karyotypes were present in 21 of 78 cases (26.9%) and structural anomalies were diagnosed in 12 of 57 cases with normal karyotypes (21.05%).

Cardiac defects are the most common fetal structural defects, both in the general pregnant population and in the population with increased NT. The prevalence of major cardiac defects increases with increasing NT values[10]. An NT thickness ≥3.5 mm in a chromosomally normal fetus has been correlated

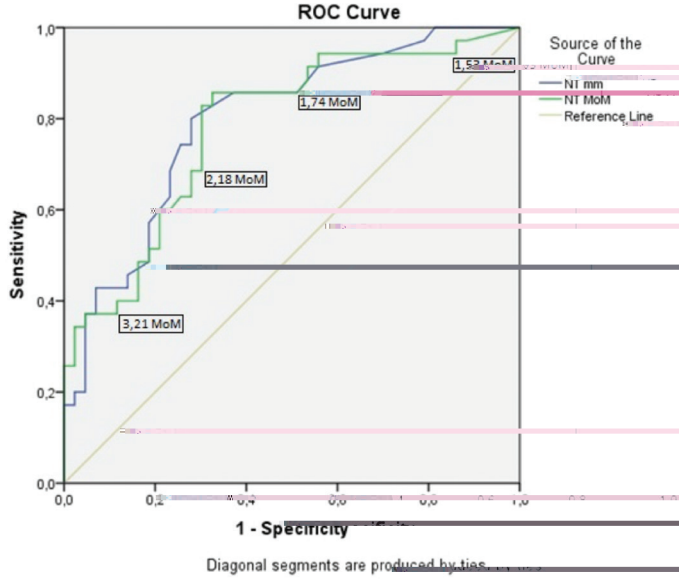

Figure 2. ROC curves of nuchal translucency measurements as MoM and millimeters for the whole study group (n=78)

ROC: Receiver operating characteristic, MoM: Multiples of median, NT: Nuchal translucency

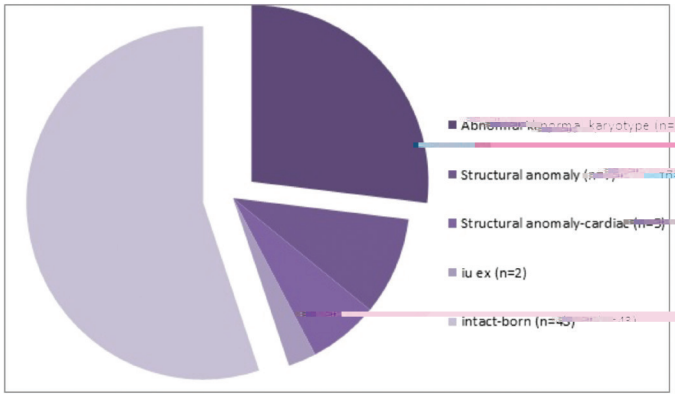

Figure 3. Increased nuchal translucency (NT) and perinatal outcomes [increased NT >1.5 MoM (n=78)]

MoM: Multiples of median

with a prevalence of congenital cardiac anomalies of 23 per 1000 pregnancies.[11] In another study, the prevalence of congenital heart disease was about 0.5% in fetuses with NT < median; 1% for NT between median and 95th percentile, 2% for NT between 95th and 99th percentiles, and increased to 3.5%, 6.5%, and 12.5% for NT of 3.5-4.4 mm, 4.5-5.4 mm, and ≥5.5 mm, respectively[12].

In our study, an increased NT was accepted as ≥1.5 MoM, and cardiac anomalies were observed in 9.6% (5/57) of fetuses with normal karyotypes, similar to the rate reported by Muller et al.,[13] higher than that found by Mavrides et al.,[14] and lower than that reported by Hyett et al[15]. If we had taken the cut-off value as 3.5 mm, cardiac anomaly rate in fetuses with increased NT and normal karyotypes would be 11.8% (4/34); however, one case would be missed with an NT measurement of 2.4 mm.

In the current study, intrauterine exitus occurred in two fetuses (2.5%) with neither abnormal karyotypes nor structural defects. Lithner et al., [9] also reported one case of intrauterine exitus (0.7%) with a normal karyotype and detailed scanning results.

The overall incidence of fetal anomalies or loss in our study was 44.8% (35/78). We defined ≥1.5 MoM as increased NT, and observed a higher risk for anomalies or loss in fetuses above this cut-off compared with other studies that reported adverse outcome rates ranging between 11% and 25.9% for fetuses with increased NT, even though their cut-offs were most probably higher than ours in millimeters because of the differences in the definitions of increased NT.[9,16-18] Abnormal fetal karyotype, congenital structural anomalies, and intrauterine fetal death were accepted as adverse fetal outcomes in our study. Souka et al.,[16] observed chromosomal anomalies in 64.45% of fetuses with NT measurements ≥6.5 mm, and when karyotype was normal, the rate of live births with no defects in this group was 31.2%. According to the ROC curve analysis in our study, cases with NT >7 mm or NT MoM >4.27 invariably resulted in adverse fetal outcomes.

The preterm birth rate in the current study was 13.9%, including four multiple pregnancies. The preterm birth rate for singletons at our center is 12%, compared with 12.6% among pregnancies subjected to invasive procedures, including multiple pregnancies.[19,20] These data suggest that increased NT did not significantly increase the preterm birth rate. Pihl et al.,[21] observed a significant relationship between increased NT and preterm birth, with a cut-off value ≥2.0 mm, and Krantz et al., [22] found a significant relation between NT ≥1.96 MoM (99th centile) and preterm birth (<34 weeks). However, Dugoff et al.[23] found no relationship between increased NT and preterm birth (<37 or ≤32 weeks).

Some studies in the literature have investigated the association between NT and birth weight[22,24-28]. Earlier studies found no relationship between NT and SGA[22]. However, more recent studies have revealed an association between NT and SGA/LGA. Poon et al.,[24] demonstrated that birth weight increased with increasing fetal NT, and Papastefanou et al.[26] found that the difference between the observed and expected values of NT was related to both SGA and LGA. Kelekci et al.,[27] reported increased NT in macrosomic fetuses, whereas Weissmann-Brenner et al.,[28] found a correlation between increased NT and LGA neonates in term non-diabetic patients. In our study, the rates of SGA and LGA among cases without fetal anomalies or loss, despite increased NT, were 13.9% and 4.7%, respectively. The apparent discrepancies between these rates and those of other recent studies may be attributable to the small sample sizes.

We were unable to diagnose any specific syndromes in our study group, but we speculate that they could have existed among the fetuses terminated for multiple anomalies. Furthermore, we only performed conventional karyotyping and did not conduct array comparative genomic hybridization (aCGH) or other advanced genetic tests. However, a previous systematic review and meta-analysis of 17 publications found that genomic microarray analysis identified a 5% incremental yield in fetuses with increased NT and normal karyotype[29]. This technology could thus help to explain the genetic basis of some of the congenital anomalies and intrauterine deaths.

Increased first-trimester NT necessitates conventional fetal karyotyping, followed by aCGH in cases with normal karyotype results if possible. In recent years, cell-free DNA in maternal serum has appeared to be a highly sensitive screening modality for aneuploidies; however, it is not sufficient in the evaluation of increased first-trimester NT due to the need for confirmation of the positive results and the possibility of false negatives, and also its wide spectrum of etiologies. Whole-exome sequencing may become the preferred technique for investigating fetuses with normal karyotypes and/or normal aCGH in the future. Early detailed scanning and fetal echocardiography between the 14th and 16th gestational weeks are advised in the event of increased NT, and both scans should be repeated at gestational week

18-22 if the results are normal. According to the ROC curves in our study, the optimal cut-off values for NT measurements for predicting fetal anomalies or loss were 3.05 mm and 2.02 MoM. Given that one out of five fetuses with cardiac anomalies in our series had an NT thickness <3.5 mm, we suggest that fetal echocardiography could be considered for NT thickness ≥3.5 mm, which corresponds to the 99th percentile at 11-13^{6} gestational weeks, and for all cases with NT thickness ≥1.5 MoM. Infection screening might also be an option for fetuses with increased first trimester NT measurements, though infections are not frequently diagnosed, and a rate of only 1.4% was reported by Sebire et al.[30] Although, few studies in the literature indicate that apparently normal newborns with increased first trimester NT and normal karyotype do not differ from the general population regarding long-term adverse outcomes,[31] more long-term studies may provide further valuable information.

Conclusion

NT measurement is considered to be an important tool in antenatal follow-up. Higher NT measurements are associated with poorer pregnancy outcomes according to our study as well as the studies in the literature. We have observed that all cases with NT measurements >7 mm or NT MoM >4.27 had either chromosomal or structural anomalies or resulted with intrauterine fetal exitus. Our study also indicates that fetal echocardiography must be considered as a part of the assessment for all cases of NT thickness ≥1.5 MoM.

Ethics

Ethics Committee Approval: This study was approved by the Institutional Review Board and Ethics Committee of Başkent University (approval no: KA09/296).
Informed Consent: Obtained from patients.
Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.B.Y., Ç.G., N.Ş.U., Z.Y.Ç., Concept: F.B.Y., Z.Y.Ç., Design: F.B.Y., Ç.G., N.Ş.U., Data Collection or Processing: F.B.Y., N.Ş.U., Analysis or Interpretation: F.B.Y., N.Ş.U., Literature Search: F.B.Y., Ç.G., N.Ş.U., Z.Y.Ç., Writing: F.B.Y., N.Ş.U.
Conflict of Interest: No conflict of interest was declared by the authors.
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Associations between night eating syndrome and metabolic parameters in pregnant women

Gebelerde gece yeme sendromu ve metabolik parametreler arasındaki ilişki

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Abstract

Objective: In this study, we aimed to evaluate the incidence of night eating in pregnancy and the relationship between night eating scores and nutritional status, insulin resistance, and lipid profile in pregnant women.

Materials and Methods: In this study, 148 pregnant women who presented to the Gynecology and Obstetrics Clinics at Konya Training and Research Hospital in Konya were divided into two groups according to their night eating scores. These two groups were compared in terms of their nutritional attitudes and metabolic parameters.

Results: Comparisons of participants meeting night eating syndrome (NES) scores versus women without NES indicated that patients with NES exhibited fever hunger at breakfast time, more breakfast skipping ($p<0.05$) than those without NES. Also homeostatic model assessment insulin resistance, insulin, and high-density lipoprotein cholesterol parameters were significantly higher in pregnant women in the NES group ($p<0.05$). Also, correlations were found between higher night eating questionnaire total scores and higher HbA1c, insulin resistance, insulin, and more breakfast skipping.

Conclusion: The results of this study suggest that night eating symptoms during pregnancy may increase and this is able to effect glucose metabolism.

Keywords: Night eating syndrome, pregnancy, metabolic parameters in pregnancy

Öz

Amaç: Bu çalışmada, gebe kadınlarda gece yeme insidansını belirlemeyi ve gece yeme skorları ile beslenme durumu, insülin direnci ve lipit profili arasındaki ilişkiyi değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Bu çalışmada Konya Eğitim ve Araştırma Hastanesi Kadın Hastalıkları ve Doğum Kliniği'ne başvuran 148 gebe gece yeme puanlarına göre iki gruba ayrıldı. Bu iki grup, beslenme tutumları ve metabolik parametreleri açısından karşılaştırıldı.

Bulgular: Gece yeme sendromu ölçütlerini karşılayan katılımcıların karşılamayanlara göre kahvaltı saatlerinde daha az aç hissettiklerini, fazla kahvaltı atladıklarını ($p<0,05$) göstermiştir. Ayrıca gece yeme skorları yüksek gebelerde insülin direncinin homeostatik model değerlendirmesi, insülin ve yüksek yoğunluklu lipoprotein kolesterol parametreleri anlamlı olarak yüksek bulundu ($p<0,05$). Ayrıca yüksek gece yeme ölçeği toplam skorları ile daha yüksek HbA1c, insülin direnci, insülin ve kahvaltı öğününü atlaması arasında korelasyon bulundu.

Sonuç: Bu çalışmanın sonuçları gebelik sırasında gece yeme semptomlarının artabileceğini ve bunun glikoz metabolizmasını etkileyebileceğini düşündürmektedir.

Anahtar Kelimeler: Gece yeme sendromu, gebelik, gebelikte metabolik belirteçler

PRECIS: There is an increase in night eating symptoms during pregnancy and this is able to affect glucose metabolism.

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Introduction

Night eating syndrome (NES) is a disorder characterized by evening hyperphagia and nocturnal ingestion, in addition to sleep and mood disturbances[1]. Evening hyperphagia is generally defined as the consumption of more than 25% of the daily calories after dinner[2]. In addition to these symptoms, patients may experience insomnia, a severe urge to eat at night, with morning anorexia or breakfast skipping[3]. For this reason, eating at night is a complex syndrome involving poor nutrition, disordered sleep patterns, and depressed mood. NES has been found associated with eating disorder (ED) attitudes and poor physical and psychosocial functioning[3-6]. Furthermore, people with NES have a relatively high risk of obesity, inadequate glycemic control (HbA1c values >7%), and having two or more diabetic complications[7]. The prevalence of NES in the adult population was reported as 1-1.5%. Although this syndrome is seen in non-obese subjects, it is more prevalent among obese individuals (6-42%), especially for attenuation therapy[4,8,9].

Pregnancy can lead to an increase in night eating due to both the effect of metabolic changes and disturbed sleep patterns. Healthy nutrition and weight control knowledge during pregnancy have a great effect on the prevention of pregnancy complications. The detection of night eating problems in pregnant women is important for preventing health problems that many pregnant women and babies will be exposed to. This is the first study to highlight the relationship between NES and metabolic problems such as insulin resistance and lipid profile in pregnant women. Determining this relationship is important for preventive medicine. Thus, the aims of this study were to determine the incidence of night eating in pregnancy, and to determine the relationship between night eating scores and insulin resistance, lipid profile, and nutritional status in pregnant women.

Materials and Methods

Participants and procedure

A total of 148 women with singleton pregnancies were recruited from Gynecology and Obstetrics Clinics at Konya Training and Research Hospital in during their medical appointments between June 2017 and June 2018. They were at least 18 years of age. Pregnant women who were on chemotherapy or psychotropic drugs or who had diabetes mellitus were excluded from the study. All participants gave written informed consent. This study was conducted according to the guidelines laid down in the Declaration of Helsinki. Ethical approval was obtained from the Necmettin Erbakan Univercity Medical Faculty Ethics Committee Review Board (approval no: 2017/1066).

Measures

Interviews and measurements were conducted in the clinics at recruitment and at 28-38 weeks' gestation. Data on hunger scores in the morning and at night before sleep, breakfast skipping, and night eating scores were collected.

Hunger scores in the morning and at night during pregnancy were assessed using structured interviewer-administered questions: hunger scores were assessed by asking the question "How much do you feel hungry when you wake up?" The women were asked to choose one of 6 scores: 1) Empty; weak and light-headed. Your body is begging for food and you start to feel dizzy and nauseous. 2) Over-hungry. You feel irritable and unable to concentrate. You may even feel nauseous. 3) Hunger awakens. Slightly uncomfortable. You are just beginning to feel signs of hunger. Your body is giving you the signal that you might want to eat. 4) Neutral/comfortable. You are more or less satisfied, but could eat a little more. Your body has enough fuel to keep it going and is physically and psychologically just starting to feel satisfied. 5) Completely satisfied. A little bit uncomfortable. You are past the point of satisfaction, yet you can still "find room" for a little more. Your body says "no" and your mind says "yes" to a few more bites. 6) Stuffed. Very uncomfortably full. You feel heavy, tired, and bloated. Higher scores reflect feeling more full.

For determining the NES, the Night Eating Questionnaire (NEQ)[10] was used. Atasoy et al.,[11] evaluated the reliability and validity of Turkish version of the NEQ. The NEQ is a 14-item self-report measure of NES that results in a total score with higher scores reflecting greater night eating pathologies. One item, item 13, does not assess NES pathology, but rather is used as a rule-out for sleep-related ED, and it is therefore not included in the total score calculation. A cut-off of 25 has been used to screen for NES using this measure[10]. In the standardization samples, the mean total scores on the NEQ were 32.4 [standard deviation (SD): 6.8] for patients with NES and 16.0 (SD: 6.3) for patients with obesity without NES who presented for bariatric surgery. The NEQ is composed of four factors (nocturnal ingestions, evening hyperphagia, morning anorexia, and sleep/mood). Each factor is represented by three items, with the exception of the nocturnal ingestions factor, which has five items. Each item has five response options, which are coded from 0 to 4, with higher scores reflecting greater impairment.

The weight and health status of the newborns were obtained from the medical charts of infants.

Blood sample analysis

The analyses were performed in the Clinic of Biochemistry, Konya Training and Research Hospital. The plasma concentrations of the following parameters were analyzed: fasting glucose, fasting insulin, hemoglobin A1c, lipid profile, hemogram, and vitamin D. Insulin resistance, estimated by the homeostatic model assessment-method (HOMA-IR) for glucose metabolism, serum total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) for lipid metabolism.

Insulin concentrations were measured using a chemiluminescent method with a Siemens immulite 2000 xPi immunoassay analyzer (Siemens Inc.). Serum glucose and lipid concentrations were analyzed with Beckman Kits using Beckman Coulter AU 5800 biochemical analyzer (Beckman Coulter, Inc., USA). Glucose was measured using a glucose-6-phosphate dehydrogenase enzymatic assay. Triglycerides, total cholesterol, and HDL-C concentrations were determined using enzymatic colorimetry. LDL cholesterol was calculated using the Friedewald equation.

Vitamin D was analyzed using an automatic immunoassay with an Abbott Kits (Abbott Laboratories, IL 60064, USA) on architect plus i2000SR analyzer. HbA1c was determined using high-performance liquid chromatography (Trinity Biotech Premier 9210, USA).

Statistical Analysis

All statistical analyses were performed using the SPSS version 16.0 software (IBM, Chicago, IL). The Mann-Whitney U test was used to compare the related blood parameters between the non-NES and NES group. Spearman correlations were used to determine the correlation between the night eating score with demographic, glucose metabolism, and lipid metabolism parameters. P<0.05 was considered statistically significant.

Results

Characteristics of the participants

A sample of 148 pregnant women (mean age 28.4 years, SD: 5.88, range 18-44 years) were included in this study. The average body mass index (BMI) was 30.66 kg/m^2 (SD: 4.42, range 24.26-40.00 kg/m^2).

The mean hunger score in the morning before breakfast was 2.75 (SD: 1.87), and 15% of participants scored more then 4, which means really full. The mean night hunger score was 3.61 (SD: 2.11), and 36% of participants scored more then 4, meaning that they were really full.

No significant differences in maternal characteristics were observed for age, BMI, and night eating score between women with and without NES (all p≥0.05). Morning hunger scores and breakfast skipping were significantly higher in the NES group compared with the non-NES group.

The mean score on the NEQ was 16.53 (SD: 5.88, range: 5-35) using a cut-off of 25 on the NEQ;[12] 11.48% (n=17) of the participants met the criteria for NES. The means of the NES and non-NES group scores were 32.21 (SD: 5.52, range: 25-35) and 14.51 (SD: 4.78, range: 5-24), respectively.

Comparison between NES and non-NES

Comparisons of participants meeting NES criteria versus those who did not meet the criteria (Table 1) indicated that patients with NES exhibited fever hunger at breakfast time, and more breakfast skipping than pregnant women without NES (p<0.05). Also HOMA-IR, insulin, TC, and HDL-C parameters were significantly higher in pregnant women in the NES group (p<0.05). Fetal weights of the NES group were heavier than in the non-NES group, but the difference was not significant.

Correlations with night eating

Correlations between night eating with lipid profile, vitamin D, and glucose metabolism variables are described in Table 2. Significant small to large correlations were found between higher NEQ total scores and higher HbA1c, insulin resistance, insulin, more breakfast skipping, and feeling full before breakfast.

Discussion

This study investigated the prevalence of night eating in the third timester of pregnancy, and also determined the relationships among night eating symptoms and relevant metabolic variables in this population.

In this study, 11.5% of participants met the screening criteria for NES, which were determined using the NEQ. As expected, the mean score in our study was higher than the mean scores

Table 1. Comparison between pregnants with and without NES

	NES (n=17)	Non-NES (n=131)	p value
Age (years)	27.39 (4.81)	29.08 (6.76)	0.205
BMI (kg/m^2)	29.56 (4.41)	30.87 (4.39)	0.288
NE score	32.21 (5.52)	14.51 (4.78)	<0.001
Morning hunger score	2.77 (0.82)	2.50 (0.67)	0.042
Night hunger score	3.80 (0.94)	3.36 (1.21)	0.069
Skipping breakfast (day in a week)	4.38 (2.98)	2.98 (2.35)	0.003
Glucose metabolism			
Insulin (mIU/L)	9.74 (5.50)	6.97 (4.78)	0.012
Glucose (mg/dL)	89.08 (11.96)	84.99 (10.72)	0.083
HOMA-IR	2.98 (2.27)	1.60 (1.46)	0.001
HbA1c (%)	5.38 (0.39)	5.47 (0.43)	0.234
Lipid metabolism			
TC (mg/dL)	272.70 (45.87)	252.62 (47.20)	0.031
LDL (mg/dL)	152.39 (41.22)	144.63 (36.98)	0.321
HDL (mg/dL)	66.78 (10.44)	61.66 (13.01)	0.021
Vitamin D (µg/L)	13.10 (9.22)	12.18 (8.89)	0.648
Fetal weight (g)	3197.3 (389.11)	3364 (588.31)	0.098

Values are expressed as mean ± standard deviation. HOMA-IR: Homeostatic model assessment insulin resistance, TC: Total cholesterol, LDL: Low-density lipoprotein cholesterol, HDL: High-dencity lipoprotein cholesterol, BMI: Body mass index, NES: Night eating syndrome, NE: Night eating

of 4.5% and 4.6% in the healthy control studies. Other studies that used the NEQ as the measure of night eating in patients with diabetes found prevalence of NES as 7%, 8.4%, and 9.7%[13-15]. NES is a relatively common problem in morbidly obese individuals, and a definite diagnosis of NES was present in 10% of the obese group[16]. The wide range of prevalences reported across studies can be explain by the difference of assessment methods and the differences between participants in the groups. This study shows that pregnant women may have an increased tendency to night eating.

In regard to eating habits, the results indicated that increased night eating was associated with decreased morning hunger and increased breakfast skipping. This is consistent with a study of patients with diabetes that found increased breakfast skipping in patients with NES[14].

According to our results in pregnant women, increased night eating scores are associated with increased insulin resistance. This is consistent with studies of patients with diabetes that found that increased NES was associated with poorer glycemic control[7,14,16]. Evidence of the relationship between night eating and glycemic control is mixed, possibly due to differences in symptom measurement and study samples. For example, Allison et al.,[12] measured night eating symptoms using the NEQ and found no difference in HbA1c values in the NES and non-NES groups. However, in another study, Loy et al.,[17] showed that increased night hunger and a reduced number of meals in the second trimester of pregnancy resulted in a decrease in fasting blood glucose and 2nd hour of postprandial glucose. It has been observed that fasting for 10 hours in the control of the gestational glycemia is effective[18]. Gestational hyperglycemia contributes to a long-term risk for obesity in childhood,[19] neonatal adiposity, and negative perinatal outcomes[20]. These risks occur even at blood glucose concentrations below the diagnostic limit for gestational diabetes mellitus. There is evidence that moderate glycemic recovery improves perinatal outcomes in pregnant women with mild glucose intolerance[21]. To date, dietary approaches to glycemic control have mostly focused on dietary quantity and quality. However, keeping the eating time range within certain limits may offer an innovative and feasible strategy to prevent gestational hyperglycemia[22]. Night-eating behavior can harm glycemic control, sleep patterns, and weight control in pregnant women[23].

Table 2. Correlations with NES

	NE score correlation coefficient	P
Age (years)	-0.055	0.521
BMI (kg/m^2)	0.036	0.673
Morning hunger score	-0.235	0.006
Night hunger score	0.181	0.037
Skipping breakfast (day in a week)	0.201	0.012
Glucose metabolism		
Insulin (mIU/L)	0.289	0.001
Glucose (mmol/L)	0.054	0.530
HOMA-IR	0.261	0.002
HbA1c (%)	0.167	0.048
Lipid metabolism		
TC (mg/dL)	0.120	0.156
LDL (mg/dL)	0.031	0.718
HDL (mg/dL)	0.185	0.028
Hemogram	0.034	0.690
Vitamin D (µg/L)	-0.027	0.711
Fetal weight (g)	140	0.123

TC: Total cholesterol, HOMA-IR: Homeostatic model assessment insulin resistance, LDL: Low-density lipoprotein cholesterol, HDL: High-density lipoprotein cholesterol, BMI: Body mass index, NES: Night eating syndrome NE: Night eating

Our data confirm no association between NES and BMI in pregnant women. In a cross-sectional study of participants with diabetes, participants with NES had higher BMI and they were more likely to have unsatisfactory metabolic control. This evidence does not hold true in the obese population; Calugi et al.,[16] found no differences in the prevalence of the metabolic syndrome and in its individual components between participants with and without NES. The prevalence of metabolic syndrome in the obese population is already high, so it is difficult to implicate an additional effect of NES. EDs affect about 5-7% of women of chilbearing age. Previous studies have shown that the effect of pregnancy on ED symptoms largely remains unclear. Eating behavior in women with a history of anorexia nervosa may improve with pregnancy but appears to revert to prepregnancy concentrations[24]. Bulimia nevrosa symptoms during pregnancy have shown mixed results, there is evidence for worsening,[25] but also for improvement of bulimia nevrosa symptoms during pregnancy[26,27]. A study of Crow et al.,[28] showed that pregnancy had an improving effect on binge eating and purging in women who had had eating desorders before pregnancy. In another study, the proportion of women meeting criteria for binge ED was found to increase during pregnancy.

Study Limitations

The literature is limited to EDs such as anorexia, bulimia, and binge eating. In our study, it is seen that NES does not tend to improve in pregnancy in contrast to other EDs.

Conclusion

To our knowledge, no studies of night eating symptoms during pregnancy have been conducted. The results of this

study suggest that night eating symptoms during pregnancy may increase and this is able to affect glucose metabolism. Our findings can be evaluated as follows: pregnancy can lead to changes in eating attitudes and behaviors, even in women without EDs. Future research in this area should use larger samples to examine the possibility of metabolic effects of NE symptoms during pregnancy.

Ethics

Ethics Committee Approval: Approval for the study was by the Necmettin Erbakan University Faculty of Medicine Ethics Committee (approval no: 2017/1066), and all procedures were performed in accordance with the Helsinki Declaration.
Informed Consent: Informed consent was obtained from all study participants.
Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.Ö., Concept: F.K.S., C.D.D., S.Ö., Design: F.K.S., M.A.E., Data Collection or Processing: S.Ö., C.D.D., Analysis or Interpretation: F.K.S., C.D.D., Literature Search: C.D.D., M.A.E., Writing: F.K.S., C.D.D.
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First trimester complete blood cell indices in early and late onset preeclampsia

Erken ve geç başlangıçlı preeklampside ilk trimester tam kan sayım parametreleri

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Abstract

Objective: This study aimed to compare the first trimester complete blood count (CBC) indices of pregnancies complicated by early-onset preeclampsia (EOPE) or late-onset preeclampsia (LOPE).

Material and Methods: A retrospective case-control study was conducted with 186 patients. Patients were classified into three subgroups: EOPE, LOPE, and control groups. First trimester CBC results were obtained for each patient. Hemoglobin, hematocrit, red blood cell distribution width, mean corpuscular volume, white blood cell (WBC) count, neutrophil, eosinophil, basophil, lymphocyte, monocyte, mean platelet volume, platelet distribution width, plateletcrit, and platelet count were compared. The neutrophil lymphocyte ratio was calculated by dividing the absolute lymphocyte count by the absolute neutrophil count. The platelet lymphocyte ratio was calculated by dividing the absolute lymphocyte count by the absolute platelet count.

Results: The total number of cases was 21, 42, and 123, in the EOPE, LOPE, and control groups, respectively. There were statistically significant differences in the total WBC and neutrophil counts between the three groups (both $p<0.05$). WBC and neutrophil counts were found to be highest in the EOPE group, and the LOPE group had higher levels compared with controls. The optimal cut-off values to predict EOPE for WBC and neutrophil counts were 9.55×10^3/µL (sensitivity 71.4% and specificity 70.7%) and 6.45×10^3/µL (sensitivity 66.7% and specificity 74.8%), respectively.

Conclusion: Increased first trimester WBC and neutrophil counts may be predictive for EOPE.

Keywords: Early onset preeclampsia, late onset preeclampsia, complete blood count, white blood cell count, neutrophil count

Öz

Amaç: Bu çalışma ile erken başlangıçlı preeklampsi (EOPE) veya geç başlangıçlı preeklampsi (LOPE) ile komplike olan gebeliklerin ilk trimester tam kan sayımı (CBC) parametrelerinin karşılaştırılması amaçlanmıştır.

Gereç ve Yöntem: Retrospektif olarak 186 hasta ile olgu kontrol çalışması yapıldı. Hastalar EOPE, LOPE ve kontrol grubu olmak üzere üç alt gruba ayrıldı. Her hasta için ilk trimester CBC sonuçları incelendi. Hemoglobin, hematokrit, kırmızı kan hücreleri dağılım genişliği, ortalama korpüsküler hacim, beyaz kan hücresi (WBC), nötrofil, eozinofil, bazofil, lenfosit, monosit, ortalama trombosit hacmi, trombosit dağılım genişliği, platelekrit ve trombosit sayımı karşılaştırıldı. Nötrofil lenfosit oranı, mutlak lenfosit sayısının mutlak nötrofil sayısına bölünmesiyle hesaplandı. Trombosit lenfosit oranı, mutlak lenfosit sayısının mutlak trombosit sayısına bölünmesiyle hesaplandı.

Bulgular: Toplam olgu sayısı EOPE, LOPE ve kontrol gruplarında sırasıyla 21, 42 ve 123 idi. Üç grup arasında toplam WBC ve nötrofil sayısı açısından istatistiksel olarak anlamlı fark saptandı ($p<0,05$). WBC ve nötrofil sayıları EOPE grubunda en yüksek, LOPE grubunda ise kontrollere göre daha yüksek bulundu. WBC ve nötrofil sayısı için EOPE'yi tahmin etmek için en uygun kesme değerleri sırasıyla $9,55\times10^3$/µL (duyarlılık %71,4 ve özgüllük %70,7) ve $6,45\times10^3$/µL (duyarlılık %66,7 ve özgüllük %74,8) idi.

Sonuç: Artan birinci trimester WBC ve nötrofil sayıları EOPE için öngörücü olabilir.

Anahtar Kelimeler: Erken başlangıçlı preeklampsi, geç başlangıçlı preeklampsi, tam kan sayımı, beyaz kan hücre sayısı, nötrofil sayısı

PRECIS: The optimal cut-off values to predict early onset preeclampsia for white blood cells and neutrophil counts were 9.55×10^3/µL (sensitivity 71.4% and specificity 70.7%) and 6.45×10^3/µL (sensitivity 66.7% and specificity 74.8%).

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Introduction

Preeclampsia is an important public health problem that is defined as new onset hypertension and proteinuria after the 20th gestational week. Hypertensive disorders of pregnancy occur in almost 10% of all pregnancies, and the prevalence of preeclampsia is approximately 3-5% worldwide[1,2]. Recently, preeclampsia was classified into two subgroups according to the onset time of clinical findings and symptoms. Early-onset preeclampsia (EOPE) refers to disease that occurs before the 34th gestational week, whereas after 34 weeks of pregnancy, the disease is commonly referred to as late-onset preeclampsia (LOPE)[3,4]. The prevalence of LOPE is reported to be almost seven-fold higher than that of EOPE (2.72% vs. 0.38%)[4].

Early- and late-onset preeclampsia are the consequences of different underlying pathophysiologic conditions. Placentation defects, which are attributable to defective syncytiotrophoblast invasion and abnormal remodeling of the spiral arteries, are associated with early-onset disease. On the other hand, LOPE usually occurs in the presence of maternal endothelial dysfunction, which is associated with more favorable neonatal outcomes compared with EOPE. Briefly, EOPE seems to be a placental disorder, whereas LOPE is typically linked to maternal factors[3,5].

The complete blood count (CBC) is a cheap and easily accessible test that shows the cellular elements of the blood. This simple test provides valuable information about the immune system. The distribution of the different blood cell components was reported to be relevant in assessing certain obstetric complications including preeclampsia, preterm delivery, and preterm premature rupture of membranes[6,7]. Parameters such as leukocytosis, the neutrophil lymphocyte ratio (NLR), the platelet lymphocyte ratio (PLR), mean platelet volume (MPV), and red blood cell distribution width (RDW) have been shown to be associated with inflammation, and various studies have reported changes in these values according to disease processes[8-10].

Many studies in the literature have focused on comparing first trimester CBC indices between severe and mild preeclampsia[11,12]. However, we decided to conduct our study based on the onset of preeclampsia, which is a new and popular topic in perinatal medicine. Therefore, the objective of this study was to show the first trimester CBC parameter differences in pregnancies complicated by EOPE and LOPE.

Materials and Methods

This was a retrospective case-control study of 186 pregnant women who gave birth at Hacettepe University Hospital between January 2012 and December 2017. The study was approved by the Hacettepe University Non-Interventional Clinical Researches Ethics Board (approval no: GO18/358). The study was conducted in accordance with the World Medical Association Declaration of Helsinki regarding the ethical conduct of the research.

Preeclampsia diagnosis was made in accordance with the 2013 report of the American College of Obstetricians and Gynecologists, as follows: (i) new onset of hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg) after 20 weeks of gestation in a previously normotensive patient and (ii) proteinuria on urinalysis (≥300 mg/24 hour or dipstick ≥1+) or (iii) end-organ symptoms/findings (thrombocytopenia, altered serum creatinine level, increased liver transaminases, pulmonary edema, or cerebral or visual symptoms)[13] . Preeclampsia diagnosed before the 34th gestational week was defined as EOPE, while it was defined as LOPE after the 34th gestational week[3].

The study subjects were divided into the EOPE, LOPE, and control groups according to the criteria explained above. The control group was randomly selected from the computerized hospital database. This group was composed of healthy pregnancies without any maternal or fetal complications (e.g. gestational diabetes, preterm delivery, congenital malformations). Pregnant women with chronic diseases, cigarette smoking, alcohol consumption or any drug use were excluded from the study. Gestational age was estimated by the last menstrual period and confirmed using the first trimester crown-rump length measurement.

First trimester CBC testing is a routine part of first trimester follow-up in our institution. Venous blood samples were transferred into K2-EDTA tubes, and a UniCel DXH800 fully automated cell counter (Beckman Coulter Inc., US) was used for the CBC. The results of the red cell parameters, including hemoglobin (Hb), hematocrit (Htc), RDW, mean corpuscular volume (MCV), the white blood cell (WBC) count and subtypes (neutrophil, eosinophil, basophil, lymphocyte, and monocyte), and the thrombocyte indices (MPV, platelet distribution width (PDW), plateletcrit, and platelet count) were collected for each patient from the computerized hospital database. The NLR was calculated by dividing the absolute lymphocyte count by the absolute neutrophil count. PLR was calculated by dividing the absolute lymphocyte count by the absolute platelet count. If there were two or more CBC results for the same patient, we used the earliest set. Maternal age, obstetric history, gestational week at birth, birth weight, and APGAR scores were also collected from the patient files.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences version 22 software package (SPSS, Chicago). The Kolmogorov-Smirnov test was used to analyze the distribution of data. Variables are given as median (minimum-maximum) or mean ± standard deviation. The three groups were compared using the Kruskal-Wallis test or one-way analysis of variance. Statistical significance was defined as a p value less than 0.05. In the EOPE group, receiver operating characteristic curves (ROC) were generated, and the area under the curve (AUC) was calculated for significant

values. The cut-off, sensitivity, and specificity were calculated using the ROC curves and Youden's index.

Results

There were 21 cases in the EOPE group, 42 cases in the LOPE group, and 123 cases in the control group. The demographic characteristics of the patients, delivery times, and neonatal findings are shown in Table 1. There were no statistically significant differences between the three groups in terms of maternal age, body mass index (BMI), and obstetric history. However, gestational age at birth, birth weight, and APGAR scores were lower in the EOPE group.

The number of babies with a 1st minute APGAR score below seven was 13 (61.9%) in the EOPE group, 3 (7.1%) in the LOPE group, and 3 (2.4%) in the control group. The number of babies with a 5th minute APGAR score below seven was 7 (33.3%) in the EOPE group, 1 (2.4%) in the LOPE group, and 0 in the control group.

In the LOPE group, 45.2% of the cases (n=19) were born between 34 and 37 weeks; the remaining 23 (54.8%) cases were born after the 37th gestational week. All neonates in the EOPE group weighed <2500 g, whereas all babies in the control group weighed >2500 g. In the LOPE group, the distribution of cases according to birth weight was 33.3% (n=14) at <2500 g, 61.9% (n=26) at 2500-4000 g, and 4.8% (n=2) at >4000 g.

Table 2 shows the findings of the first trimester CBC parameter results in each group. There were no statistically significant differences between the three groups in terms of the Hb, Htc, MCV, RDW, eosinophils, basophils, monocytes, lymphocytes, and plateletcrit. However, there was a statistically significant difference in the WBC and neutrophil counts between the three groups. The WBC and neutrophil counts were highest in the EOPE group, and the LOPE group had higher levels compared with the control group. Although the MPV and PDW values differed between the three groups, a pairwise analysis did not demonstrate any significant differences between the three groups, as shown in Table 3.

The performance of the two variables (WBCs and neutrophils) was used to identify the EOPE and control groups using the ROC analysis as shown in Figure 1. For the WBC and neutrophil counts, the AUC was 0.758 (95% CI: 0.633-0.866) and 0.749 (95% CI: 0.639-0.877), respectively, and the p values were <0.05 for both parameters. The optimum cut-off values for the WBCs and neutrophils were 9.55×10³/μL (sensitivity 71.4% and specificity 70.7%) and 6.45×10³/μL (sensitivity 66.7% and specificity 74.8%), respectively.

Table 1. Characteristics of the patients, delivery times, and neonatal findings

	Early onset (n=21)	Late onset (n=42)	Control (n=123)	p value
Maternal age	33 (21-43)	31 (20-41)	29 (19-40)	0.087
BMI	25 (20-30)	24 (21-32)	25 (21-29)	0.224
Gravida	2 (1-7)	1 (1-7)	2 (1-6)	0.322
Parity	0 (0-3)	0 (0-3)	1 (0-3)	0.359
Abortion	0 (0-5)	0 (0-3)	0 (0-3)	0.735
Living child	0 (0-3)	0 (0-3)	1 (0-3)	0.342
Gestational day at birth	225 (170-236)	259 (241-284)	271 (259-287)	<0.05
Birthweight (g)	1340 (550-2140)	2970 (1800-4750)	3380 (2530-4630)	<0.05
APGAR 1st minute	6 (0-9)	9 (5-10)	9 (4-10)	<0.05
APGAR 5th minute	7 (0-10)	10 (8-10)	10 (7-10)	<0.05

[All values are given as median (minimum - maximum)], BMI: Body mass index

Discussion

Diagnosis of preeclampsia commonly refers to the classic findings of new-onset hypertension and proteinuria in pregnant women after 20 weeks of gestation. On the other hand, EOPE and LOPE are now considered as two different disorders with unincorporated pathophysiologies. Impaired placental development in early pregnancy is mainly associated with EOPE, whereas maternal vascular instability due to endothelial injury is more typically associated with LOPE. Increased inflammation resulting from these different dysfunctions is the mutual effect, and such inflammatory

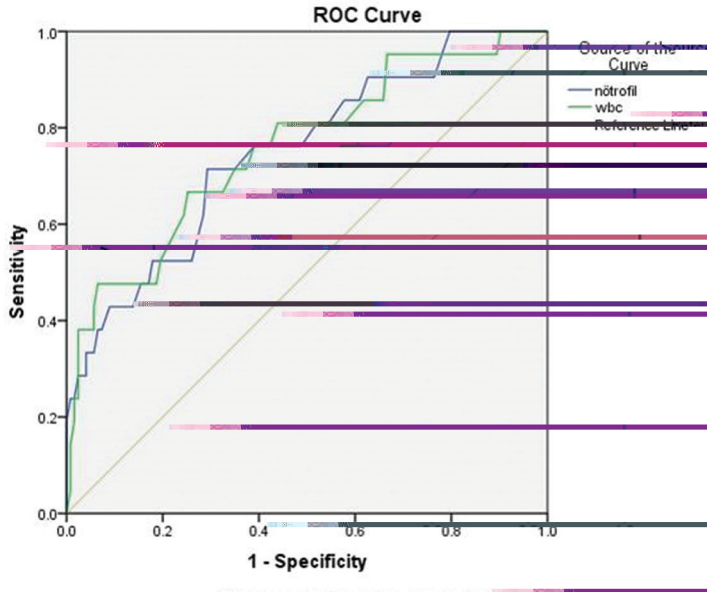

Figure 1. The performance of white blood cells and neutrophils to identify early onset preeclampsia

ROC: Receiver operating characteristic, WBC: White blood cell

changes/processes are thought to be responsible for the maternal and fetal complications[3,14].

Pregnancy is associated with certain hematologic changes such as decreased Hb, increased MCV, leukocytosis, neutrophilia, and slight thrombocytopenia[15]. Although the most common laboratory finding in preeclampsia is proteinuria, other changes (thrombocytopenia, neutrophilia, and Htc increase) may also be detected in a routine CBC[16]. Accordingly, investigators have conducted several studies to investigate the potential identification or prediction of preeclampsia and disease severity using first trimester hemogram results[11,12,17]. To the best of our knowledge, no English language article in the current literature has compared first trimester CBC values between patients with EOPE and LOPE.

Anemia is a common health problem, especially in low income countries; however, a recent systematic meta-analysis reported that anemia during the first and second trimester was not associated with preeclampsia[18]. In our study, we were also unable to find any differences in anemia parameters (Hb, Htc, MCV) between the three groups. RDW is another red cell parameter in routine CBC testing that indicates the variation in erythrocyte cell sizes. Increased RDW levels, a condition referred to as anisocytosis, are shown to be linked to inflammation in the general population. Furthermore, previous studies reported that elevated RDW levels in pregnancy were associated with the occurrence and severity of preeclampsia[11,17]. We were unable to demonstrate any difference in the RDW levels between the three groups.

Leukocytosis is a physiologic change observed in healthy pregnancies secondary to neutrophilia, and WBCs are known to be the mediator of inflammation[19]. It has been reported that first trimester leukocytosis is associated with adverse pregnancy outcomes, in particular with preterm delivery[7]. Canzoneri et al.,[20] have shown that increased total leukocyte count was associated with both preeclampsia and disease severity. According to their findings, neutrophilia was the only WBC subgroup associated with severe preeclampsia. Moreover, changes in WBC functions occur in addition to

Table 3. Pairwise comparison results for MPV and PDW (p values)

	MPV		PDW	
	Significance	Adjusted significance	Significance	Adjusted significance
EOPE vs. LOPE	0.924	1	0.926	1
EOPE vs. Control	0.111	0.332	0.022	0.067
LOPE vs. Control	0.024	0.073	0.110	0.330

MPV: Mean platelet volume, PDW: Platelet distribution width, EOPE: Early-onset preeclampsia, LOPE: Late-onset preeclampsia

Table 2. Comparison of the first trimester CBC results

	Early onset	Late onset	Control	p value
Hemoglobin (g/dL)	12.5 (9-16.9)	12.9 (7.7-14.8)	12.8 (9.3-15.5)	0.790
Hematocrit (%)	37.3 (26.2-48.8)	37.9 (26.5-44.6)	38 (30.6-43.9)	0.921
MCV	87.8 (73.6-95.7)	84.2 (53.4-97.2)	84.6 (13-92.6)	0.131
RDW (%)	13.6 (11.9-18.7)	14.1 (12.3-22.4)	13.8 (11.4-35.5)	0.210
WBC ($\times10^3/\mu L$)	10.47±2.15	9.73±2.74	8.42±1.89	<0.001
Neutrophils ($\times10^3/\mu L$)	7.58±2.04	6.84±2.62	5.79±1.51	<0.001
Eosinophils ($\times10^3/\mu L$)	0.1 (0-0.4)	0.1 (0-0.5)	0.1 (0-0.8)	0.758
Basophils ($\times10^3/\mu L$)	0 (0-0.1)	0 (0-0.2)	0 (0-0.1)	0.630
Monocytes ($\times10^3/\mu L$)	0.6 (0.3-1.1)	0.6 (0.3-1)	0.6 (0.1-7.8)	0.397
Lymphocytes ($\times10^3/\mu L$)	2 (1.2-4.1)	2.1 (1.1-3.4)	1.9 (0.7-3.7)	0.197
Platelets ($\times10^3/\mu L$)	254 (162-364)	269 (158-561)	237 (151-448)	0.052*
MPV (fL)	8.4 (7.5-10.3)	8.5 (6.9-10.6)	8.8 (6.6-12.1)	**0.039**
PDW (ratio)	16.6 (15.7-18.1)	16.6 (15.9-18)	16.8 (15.7-19.8)	**0.035**
Plateletcrit (%)	0.210 (0.141-0.320)	0.216 (0.134-0.41)	0.212 (0.125-0.343)	0.622
NLR	3.68 (1.59-9.17)	3.32 (0.83-9.23)	2.95 (0.14-7.87)	0.112
PLR	126.67 (77.32-243.08)	128.57 (53.44-291.67)	127.83 (65.94-414.29)	0.968

(Values are given as median (minimum-maximum) or median ± standard deviation)
MCV: Mean corpuscular volume, RDW: Red cell distribution width, MPV: Mean platelet volume, PDW: Platelet distribution width, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, WBC: White blood cell, CBC: Complete blood count

the elevated neutrophil levels in women with preeclampsia, and phenotypic and metabolic changes in granulocytes and monocytes have also been shown in *in vivo* studies[21]. Our findings are consistent with those of previous studies. Although an increased first trimester WBC count, which is likely due to neutrophilia, is associated with preeclampsia, the counts of eosinophils, basophils, monocytes, and lymphocytes did not differ in preeclamptic women compared with controls. In the present study, we showed that a WBC count >9.55×10^3/μL was associated with EOPE with 71.4% sensitivity and 70.7% specificity. In addition, a neutrophil count >6.45×10^3/μL was found to be useful to predict EOPE with 66.7% sensitivity and 74.8% specificity.

Insufficient placental development and remodeling are responsible from obstetric complications, which may be consequences of increased maternal immune system response to the fetal structures. The cause of increased neutrophils and WBCs in maternal blood is most probably due to this altered maternal inflammation. Activated neutrophils and WBCs secondary to the endothelial dysfunction in preeclampsia may be responsible from the increased first trimester levels of WBC and neutrophils.

Platelet indices such as platelet count, MPV, plateletcrit, and PDW are important indicators of platelet activation and thromboembolic events. Thrombocytopenia may be a late laboratory finding of preeclampsia, and low levels are usually associated with more severe disease[22]. However, several studies have reported that first trimester platelet count might not be a good marker to predict subsequent preeclampsia[12,23]. In our study, the median platelet levels in the first trimester were lower in the control group and higher in the EOPE group, but this finding was not statistically significant. Increased PDW and MPV together with decreased plateletcrit levels have been reported to be associated with preeclampsia[12]. However, Monteith et al.,[2] studied the MPV changes in each trimester and the prediction of EOPE by comparing patients with healthy subjects. However, they were unable to determine any significant first trimester MPV value for the prediction of EOPE. In contrast, first trimester MPV levels of >9.95 fL were found to be a valuable marker to predict preeclampsia in a different study[23]. According to our findings, we found no correlation between thrombocyte parameters in preeclampsia and disease onset.

NLR and PLT are two other inflammatory markers that can easily be calculated. The prognostic value of increased NLR in cardiovascular diseases has been well described in the literature,[24] and neutrophilia with a stable lymphocyte count leads to an increased NLR in preeclampsia. Several studies have suggested that an elevated NLR might be an effective marker to predict preeclampsia and disease severity[25-27]. In our study, although the NLR decreased from EOPE to controls, this was not statistically significant, most likely owing to the small number of participants. The consumption of platelets after endothelial injury results in thrombocytopenia in preeclampsia. As a result, researchers have claimed that PLR levels may decrease in preeclampsia. Generally, the results pertaining to PLR changes in preeclampsia are conflicting, with both increased[26] and decreased levels[11] reported in the literature. We were unable to demonstrate any difference between the three groups in terms of either NLR or PLR values. Minor changes in CBC parameters may not have reached statistical significance in the present study to show the changes in the NLR and PLR. Also, increased or decreased levels of neutrophils, lymphocytes, and platelets in each patient may not be enough to show a difference, and several clinical and pathologic events may be responsible for this issue. Although these two parameters are both thought to be correlated with altered inflammation, physicians should be aware of the high false and negative predictive values to predict preeclampsia in clinical practice.

Study Limitations

Missing and unreliable data due to the retrospective design of the study and the use of a single center are the main limitations of our study. The number of patients was relatively lower in the EOPE group than in the other groups, which may have affected the results. Moreover, CBC test results may have been influenced by several factors such as smoking, drug intake, and concomitant diseases and infections, and these factors may not have been disclosed by some patients.

Conclusion

In conclusion, we have demonstrated that first trimester leukocytosis and increased neutrophils are the only CBC indices associated with the onset time of preeclampsia. We did not observe any significant difference between the other inflammation markers (MPV, NLR, and PLR) in the EOPE group as compared with the LOPE group and healthy controls. Further well-designed studies with multicenter participation are warranted to ascertain the changes in first trimester CBC parameters in EOPE.

Ethics

Ethics Committee Approval: The study was approved by the Hacettepe University Non-Interventional Clinical Researches Ethics Board (approval no: GO18/358).
Informed Consent: Retrospective study.
Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.S.B., Concept: M.S.B., Design: G.Ö., Data Collection or Processing: G.Öz. , E.F., Analysis or Interpretation: D.A.H., Literature Search: A.T., Writing: G.Ö.
Conflict of Interest: No conflict of interest was declared by the authors.
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Utility of the "floating ball sign" in diagnosis of ovarian cystic teratoma

Over kistik teratoma tanısında "yüzen top işaretinin" yararlılığı

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Abstract

Objective: To evaluate the incidence of the "floating ball" sign in cross-sectional imaging modalities in patients with ovarian teratoma, and to investigate the relationship between the morphologic features of the teratoma and this sign.

Materials and Methods: Preoperative computed tomography and magnetic resonance imaging studies of 112 women with a pathologic diagnosis of ovarian mature cystic teratoma (MCT) were reviewed for the presence of the floating ball sign. Tumor size, tumor characteristics and the number, size, and characteristics of floating globules were evaluated.

Results: In 112 patients (mean age 35.5±16 years, range 5-84 years), 118 ovarian MCTs were diagnosed pathologically. The floating ball sign was demonstrated in cross-sectional imaging in 30 (25.4%) patients. Among 2 of them, MCT was associated with malignancy (squamous cell carcinoma). There was a significant relationship between the floating ball sign, tumor size, and the wall thickness of the tumor (p=0.003 and p=0.018, respectively). In linear regression analysis, a similarly significant relationship was found between the presence of this sign and tumor size and patient age (p=0.003 and p=0.035, respectively).

Conclusion: The floating ball sign, as a pathognomonic sign for the diagnosis of ovarian teratomas, seems to be more common than is known. Although this sign is almost always seen in MCTs, it may rarely be seen in teratomas with malignant transformation. The relationship of this sign with the characteristics of the tumor can provide an insight into the occurrence of these balls.

Keywords: Dermoid cyst, magnetic resonance imaging, tomography, ovary

Öz

Amaç: Over teratomlu hastalarda kesitsel görüntüleme modalitelerinde "yüzen top" işaretinin sıklığını değerlendirmek ve teratomun morfolojik özellikleri ile bu işaret arasındaki ilişkiyi saptamaktır.

Gereç ve Yöntemler: Patolojik olarak over matür kistik teratoma (MKT) tanısı alan 112 kadın hastanın bilgisayarlı tomografi ve manyetik rezonans görüntüleme çalışmaları yüzen top işareti varlığı açısından değerlendirildi. Tümör boyutu, tümör karakteristikleri ve yüzen globüllerin sayı, boyut ve karakteristikleri değerlendirildi.

Bulgular: Yüz on iki hastada (ortalama yaş 35,5±16, yaş aralığı 5-84), patolojik tanı alan 118 over MKT değerlendirildi. Kesitsel görüntüleme yöntemleri ile yüzen top işareti 30 hastada (%25,4) saptandı. Bu hastaların 2'sinde MKT malignite ile birlikte idi (skuamoz hücreli karsinoma). Yüzen top işareti ile tümör boyutu ve tümör duvar kalınlığı arasında anlamlı ilişki saptandı (sırasıyla p=0,003 ve p=0,018). Lineer regresyon analizinde, benzer şekilde yüzen top işareti varlığı ile tümör boyutu ve hasta yaşı arasında anlamlı ilişki saptandı (sırasıyla p=0,003 ve p=0,035).

Sonuç: Yüzen top işareti over teratomu tanısında patognomonik bir bulgu olup bilinenden daha sık görülmektedir. Bu işaret neredeyse tamamen MKT'de görülmekle birlikte nadiren malign transformasyon gösteren teratomlarda da görülebilmektedir. Bu bulgunun tümör karakteristikleri ile olan ilişkisi yüzen topların oluşumu hakkında bilgi verebilir.

Anahtar Kelimeler: Dermoid kist, manyetik rezonans görüntüleme, tomografi, over

PRECIS: We have evaluated the incidence and relationship of floating ball sign in ovarian mature cystic teratomas with patient age and tumor characteristics.

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Introduction

Mature cystic teratomas (MCTs) are the most commonly seen germ cell tumors of the ovary[1]. They account for at least 10% of all ovarian tumors[2].They arise from two or three primitive embryonic germ cell layers, known as the endoderm, mesoderm, and ectoderm[3]. When the ectodermal component predominates, they are called dermoid cysts[2].

Preoperative diagnosis is important because teratomas are the most common surgically excised ovarian tumor group. Imaging modalities such as ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) help us to evaluate a wide spectrum of radiologic presentations and make the correct diagnosis[4]. Although ultrasound is the first-line imaging modality in the evaluation of these tumors, diagnosis sometimes might be difficult due to the limitless combinations of different echo patterns in MCTs. Cross-sectional imaging modalities are preferred in indeterminate cases or for confirmation of teratoma suspicion in ultrasound. Fat content is the most important feature of the teratoma, which can be readily demonstrated using cross-sectional imaging. Besides that, some pathognomonic features enable the diagnosis easily. The "floating ball" sign is an uncommon pathognomonic feature that defines one or more small spherical structures floating in a cyst[5]. It may also be called the "meat ball" sign or the "truffle sign," referring to numerous small floating globules, or "pokeball" sign, referring to a single ball floating in a fat-fluid interphase[6,7]. The latter is a recent description, which is associated with the current pop culture craze regarding Pokemon balls[8].

The aim of this retrospective single center study was to assess the utility of the floating ball sign in the diagnosis of ovarian teratoma and to investigate the relationship between this rare sign and tumor morphologic features.

Materials and Methods

Patients and study setting

This retrospective study was approved by the University of Health Sciences, İzmir Tepecik Training and Research Hospital Ethics Committee (25th April 2018, no: 2018/4-9). Patients with ovarian teratoma who were surgically treated at a single tertiary care institution between August 2009 and January 2018 were reviewed. The pathology results were collected from patients' hospital records. The inclusion criteria of the study were as follows: a) All patients would have a pathologic diagnosis of teratoma originating from the ovary, b) patients would have undergone diagnostic abdominal CT or MRI before surgical resection performed with a standard protocol. After exclusion of two patients with immature teratomas and one patient with a mixed germ cell tumor including a teratoma component, a total of 112 patients with a diagnosis of MCT were enrolled in the study. All patients were diagnosed and treated in the same tertiary hospital with a gynecologic oncology department serving as a cancer center for gynecologic malignancies.

Imaging protocol

MRI examinations were performed with standard protocol using a 1.5 T MRI system (Siemens Avanto, Siemens Aera, GE Optima360) with a six-channel body coil. The protocol included sagittal, axial, and coronal T2-weighted images without fat saturation, axial T2-weighted fat saturated images, and axial T1-weighted fat saturated gradient-echo images before and after intravenous contrast administration (Gadoteric acid, Dotarem®, Guerbet, Paris, 0.1 mmol/kg).

CT examinations were performed using a 64 and 128 detector CT system in the venous phase after intravenous non-ionic contrast administration.

Data analysis

Images were re-evaluated by a radiologist (AIB) who was blinded to the clinical data, results of surgery, and pathology reports. The floating ball sign was defined as an appearance of a globular structure floating in a cyst without a direct relationship with the wall of the tumor. Radiologic image evaluation included the assessment of the tumor size, the thickness of the wall of the cystic mass, the presence of any globular structures floating in the cystic mass (floating ball sign), and the number and size of the floating balls. Tumor diameters were measured in three orthogonal planes and the maximum diameter was recorded as the largest tumor size. The presence of fat in the tumor was noted. To evaluate fat in MRI, both fat suppression techniques and chemical shift imaging including in-phase and opposed-phase imaging were used. In cases with the floating ball sign, the size and number of the balls, location of the balls in the cyst (gravity-dependent, gravity-independent or on a fat-fluid interphase), and the density of the balls and the presence of detectable fat in the balls were recorded.

Surgical evaluation

All patients underwent laparotomy and frozen section assessment for the diagnosis. Fertility-sparing surgery or hysterectomy-salpingoopherectomy was performed according to the patient's age, desire for fertility, and other circumstances such as multifibroid uterus. Pelvic lymph node dissection was performed as a part of the routine surgical procedure in 2 patients with malignant neoplasia in frozen sections. Tumors were diagnosed by clinical pathologists with more than 10 years' experience in gynecologic pathology.

Statistical Analysis

Statistical analyses were performed using SPSS version 20.0 (Chicago, IL, USA). Data are presented as mean ± standard deviation. The Mann-Whitney U test and Pearson's chi-square test were applied to evaluate the relationship between the floating ball sign, and continuous variables such as patient's age, tumor size, and tumor wall thickness. Linear regression

Table 1. Summary of patient age, maximum tumor size, and maximum tumor wall thickness in the teratoma groups with and without the floating ball sign. Results are given in mean value (range minimum-maximum)

Variable	Teratoma lesions (n=118)	
	Floating ball sign present (n=30)	Floating ball sign absent (n=88)
Patient age	40 (18-76)	34 (5-84)
Max tumor size (mm)	97 (37-220)	70 (14-197)
Max wall thickness (mm)	4.5 (1-27)	2.6 (0.7-35)

Max: Maximum

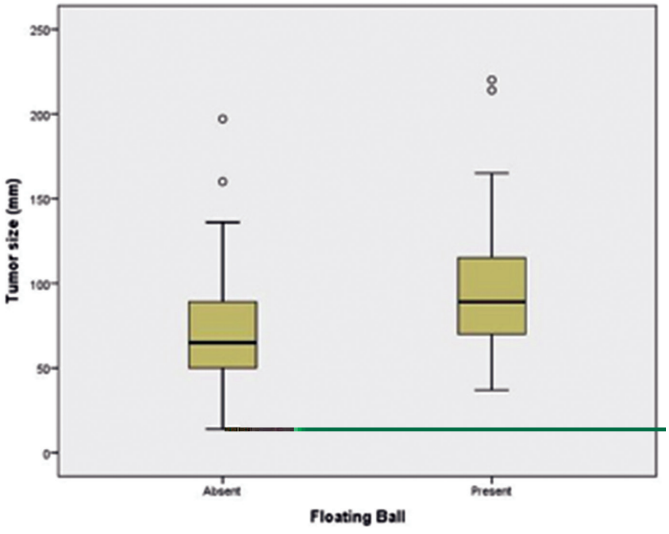

Figure 3. Box-and-whisker plots show maximum tumor size in the two groups with and without floating balls inside the cystic teratoma. Central horizontal line in box represents mean value, bottom and top edges of box indicate 25th and 75th percentiles, and vertical line indicates the range of data

Discussion

In the present study, we evaluated the incidence of the floating ball sign in our patient cohort with ovarian teratoma and investigated the relationship between this sign and tumor morphologic parameters and patient age. Our results indicate that, this sign, with a 25% incidence rate, is much more common in clinical practice than it has been reported in the literature. Floating balls in teratomas are mentioned in case reports or case series; however, the exact incidence rate of this sign is not given in the studies. As described in some of those reports, we found that this sign was usually seen in larger MCTs and in those with thicker walls. This may give some clues about the formation of these ball-like structures. Interestingly, in our series, both MCTs with squamous cell carcinoma had the floating ball sign, which has not been mentioned in the literature until now.

Atypical presentations of ovarian teratomas can be a challenge both for radiologists and gynecologists. Thanks to the fat content, classic ovarian teratomas are easily diagnosed with imaging. However, when there is no fat or it is very scarce in amount, other radiologic features, each reflecting a specific pathologic equivalent, enable the correct diagnosis[4,9].

The floating ball sign is described as a pathognomonic sign for the diagnosis of ovarian MCTs[5,10]. It was first described in 1991 by Muramatsu et al.[11] with radiologic imaging. Later, many case reports were written on this sign regarding its rarity. However, our study shows that, with a 25% incidence rate, it is not rare, contrary to popular belief. In addition, it can be easily recognized by any physician in ultrasound, CT or MRI; therefore, it may become an important sign of MCTs and may have an educational value. Besides that, in the presence of this pathognomonic sign, abbreviated MRI protocols with shorter scan duration and without intravenous contrast agent might be sufficient for the diagnosis.

Floating balls are spherules composed of variable proportions of keratin, fibrin, hemosiderin, sebaceous material, hair, and fat[5]. According to the contents, these floating spherules take a gravity-dependent or gravity- independent position in the cyst. In our study, most of the balls were located at the fat-fluid interphase. Although the mechanism of the formation of those balls is still unknown, it is speculated that, globules form by aggregation of sebaceous material around a nidus made up of debris, squames or hair shafts, while moving in the cystic cavity[5,12]. They form into discrete spherical masses because of the difference in physical and thermal properties of the material being deposited[13]. In our study, the floating ball sign was significantly related to tumor size and it was seen in somewhat larger cysts. This correlates with evidence that enough space is essential for floating balls to form their globular shape[5,14]. In addition, as Al Hilli et al.[15] proposed, the predominance of a large secretory and absorptive surface lining the cyst may favor the absorption of most of the contents causing the remaining material to solidify and mold into balls. Another variable related to the floating ball sign was the tumor wall thickness in the univariate analysis. Given that these balls are made up of keratin and sebaceous material, a thick tumor wall containing skin derivatives such as sebaceous glands may provide these materials in sufficient amounts.

We also investigated the relationship between patient age and the floating ball sign. Although the mean age of the patient group with the sign was higher, the relationship was not significant in the univariate analysis. However, in the multivariate analysis, age was significantly related to the floating ball sign. MCTs are supposed to grow at an average rate of 1.8 mm each year according to the relevant literature[1]. Our result of the linear regression analysis may be related

to that, as we expect larger tumors with increasing age. In addition, it is believed that small bowel peristaltism against the cyst wall encourages the viscostatic aggregation of the sebaceous material and promotes the formation of floating balls; therefore, time is needed for these balls to take their uniform, globular shape[6].

Another interesting finding of our study was that there were two patients with squamous cell carcinomas growing in MCTs, both of which contained floating balls. Otigbah et al.[7] claimed that the presence of hairy balls suggesting papillary projections on ultrasound might indicate a higher likelihood of malignancy; however, no related studies were found in the literature to support this proposal. According to the literature, whether globule formation occurs in both benign and malignant cysts is not known, but all cases reported thus far have been benign[14]. We cannot make a general statement about floating balls in malignant teratomas due to the insufficient number of malignant cases in the study for a statistical analysis. However, we can claim that, floating balls are not exclusively seen in benign cystic teratomas; therefore, the floating ball sign cannot be pathognomonic for benign teratomas. This is an important result of our study, challenging some other reports in the literature[6,16].

Study Limitations

There are a few limitations in the present study. First, it was a single-center retrospective study. Second, we did not include immature teratomas and mixed germ cell tumors in the study because there were only 3 cases. In addition, according to the relevant literature, the appearance of multiple floating spherules has not been found in tumors other than cystic teratomas[17]. Third, CT or MR images of the patients were assessed in the study. We believe this limitation did not cause a significant impact because the floating ball sign and fat content is easily detected in both imaging modalities. In addition, ultrasound imaging could not be compared with sectional imaging modalities due to the retrospective nature of the study. The floating ball sign was not properly noted in ultrasound reports. Lastly, the small number of malignant teratomas in the study caused a relative limitation because we could not make a statistical analysis and compare that group with benign teratomas.

Conclusion

The floating ball sign is a popular pathognomonic sign for cystic teratomas and it is much more common in clinical practice than is known. It is seen in older patients with larger teratomas. In addition to being easily assessed in every imaging modality by any physician interested in gynecologic imaging, it is of paramount importance in the diagnosis of ovarian cystic teratoma. Nevertheless, this sign can be seen in both benign and malignant MCTs. Therefore, each teratoma lesion including floating balls should be carefully evaluated for signs of malignancy.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences, İzmir Tepecik Training and Research Hospital Ethics Committee (25th April 2018, no: 2018/4-9).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Gynecology Ward Staff, Concept: H.Ş., Design: H.Ş., A.I.A., Data Collection or Processing: H.Ş., A.I.A., T.K., Analysis or Interpretation: H.Ş., A.I.A., D.A., M.S., Literature Search: H.Ş., A.I.A., Writing: H.Ş., T.K., M.S.

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Oxidative stress in cervical cancer and its response to chemoradiation

Rahim ağzı kanserinde oksidatif stres ve kemoradyasyon yanıtı

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Abstract

Objectives: Cervical cancer (CaCx) is one of the leading causes of cancer-related death among women worldwide, with the great social and economic burden. Diagnoses in early stages can decrease mortality and morbidity rates. This study was conducted to evaluate the status of serum total antioxidant capacity (TAC), and malondialdehyde (MDA) and copper concentrations among patients with CaCx to determine the level of oxidative stress and effect on which of chemoradiation.

Materials and Methods: Fifty patients with histopathologically proven CaCx who visited the department of oncology & gynaecology and 50 age-matched healthy females were selected for the study. Serum TAC, MDA, and copper were estimated in both study groups. The effect of chemoradiation on these was estimated in patients with CaCx.

Results: The mean ± standard deviation age of the patients was 43.98±6.38 years, whereas that of the controls was 31.56±6.84 years. The mean serum copper and MDA concentrations in the patients was significantly higher as compared with the controls, whereas the mean TAC in the patients was reduced when compared with the controls. After chemoradiation, there was a significant increase and decrease in TAC and MDA, respectively, after chemoradiotherapy, whereas the changes in the copper concentrations were insignificant.

Conclusion: These results suggest that patients with CaCx were in oxidative stress because the oxidative parameters in serum (copper, MDA) were increased and the defensive TAC was decreased in patients with CaCx and chemoradiotherapy improved their anti-oxidant capacity. Further studies are needed to evaluate the concurrent use of antioxidants with chemoradiotherapy for improving the disease prognosis.

Keywords: Cervical cancer, copper, malondialdehyde, total antioxidant capacity, chemoradiation

Öz

Amaç: Büyük bir sosyal ve ekonomik yükü olan rahim ağzı kanseri, dünya genelindeki kadınlar arasında kansere bağlı ölümlerin önde gelen nedenlerinden biridir. Erken evrelerdeki tanısı, mortalite ve morbidite oranlarını azaltabilmektedir. Bu çalışma, oksidatif stres düzeyini ve kemoradyasyonun etkisini belirlemek için rahim ağzı kanserli hastalarda serum total antioksidan kapasitesi (TAK) ile malondialdehit (MDA) ve bakır konsantrasyonlarının durumunu değerlendirmek amacıyla yapıldı.

Gereç ve Yöntemler: Onkoloji ve jinekoloji anabilim dalına başvuran, histopatolojik olarak rahim ağzı kanseri olduğu kanıtlanmış 50 hasta ve yaş-uyumlu 50 sağlıklı kadın çalışma için seçildi. Her iki çalışma grubunda da serum TAK, MDA ve bakır değerleri ölçüldü. Kemoradyasyonun bunlar üzerindeki etkisi rahim ağzı kanserli hastalarda değerlendirildi.

Bulgular: Hastaların ortalama yaşı ± standart sapma 43,98±6,38 yıl iken, kontrollerin ise 31,56±6,84 yıl idi. Hastalarda ortalama serum bakır ve MDA konsantrasyonları kontrollerle karşılaştırıldığında anlamlı derecede yüksek iken, ortalama TAK değeri kontrollere göre azaldı. Kemoradyoterapi sonrasında sırasıyla TAK ve MDA'da anlamlı bir artış ve azalma mevcuttu, bakır konsantrasyonundaki değişiklikler ise anlamlı değildi.

Sonuç: Bu bulgular; rahim ağzı kanserli hastaların oksidatif stres içerisinde olduklarını, çünkü bu hastalardaki serum oksidatif parametrelerin (bakır, MDA) arttığını ve koruyucu TAK'nin azaldığını ve kemoradyoterapinin antioksidan kapasitelerini artırdığını göstermektedir. Hastalık prognozunu iyileştirmede, antioksidanların kemoradyoterapi ile eş zamanlı kullanımını değerlendirmek için ileri çalışmalara gereksinim duyulmaktadır.

Anahtar Kelimeler: Rahim ağzı kanseri, bakır, malondialdehit, total antioksidan kapasite, kemoradyasyon

PRECIS: Oxidative stress among cervical cancer patients found to be increased and chemo-radiotherapy improved their anti-oxidant capacity.

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Introduction

Cervical cancer (CaCx), the third most frequently occurring cancer among women worldwide, accounted for 266,000 deaths in 2012, 87% of which occurred in developing countries[1]. CaCx is the leading cause of deaths related to cancer in India and accounts for 17% of all cancer deaths in women aged between 30 and 69 years. Taking current incidence rates into consideration, the annual load of fresh cases is expected to increase to 225,000 by 2025 in India[2,3]. The chances of surviving CaCx are considered as 42% in India[4].

The most important causative agent is human papillomavirus (HPV), which spreads through sexual intercourse; males are the carriers in most cases, infecting and generating the disease in women. Many adults are unaware of HPV infection and its associated risks[5].

HPV causes CaCx by damaging DNA, but recent data revealed that oxidative stress plays a role in its development[6]. Chemo-radiation is known to improve survival of patients with CaCx. Oxidative stress is a shift of balance towards pro-oxidants in the prooxidant-antioxidant system. Free radicals are generated with a decrease in the levels of antioxidants, which leads to DNA damage, causing dysfunction and disease[7]. Severe oxidative stress causes DNA damage and mutations of tumor suppressor genes, initializing events in carcinogenesis, in addition, promoting multi-step carcinogenesis[7-9].

Malondialdehyde (MDA) is a known marker of oxidative stress and antioxidant status in patients with cancer. The reactive oxygen species (ROS) produced by different processes initiate lipid peroxidation and lead to the production of excessive levels of MDA, which in turn changes the cellular function and leads to cancer formation[10]. The increase in MDA concentration can be attributed to a higher production of ROS due to the increased oxidative damage in patients with uterine cancer. As the disease progresses, the oxygen radical production also increases leading to increased lipid peroxidation. This results in cellular membrane degeneration and DNA damage[11]. The increase in free radical generation leads to excessive lipid peroxidation, indicated by a rise in serum MDA. Free radicals may cause evident changes to cell membrane function and the structural organization of DNA, thereby leading to mutations. Therefore, it can be stated that the product of lipid peroxidation could be one of the possible causes of uterine cancer progression[11,12].

The total antioxidant capacity (TAC) measures the antioxidant capacity of whatever antioxidants are present in a biologic sample. It can be used as a dependable biomarker for the diagnosis, prognosis, and prevention of a large number of diseases[13,14].

Copper plays a pivotal role in the oxidant-antioxidant mechanism. The imbalance of copper leads to an increased susceptibility to oxidative damage. Copper acts as a pro-oxidant and may be involved in the formation of free radicals, catalyzed by metal[15]. Copper can interact directly with the bases of DNA at the sites of guanine and cytosine[16]. *In vitro*, the addition of copper to DNA mediates extensive DNA base damage inducing more mutations[17]. Copper also reacts with other free radical species such as hydroxide ion; therefore, the inactivation or loss of certain tumor suppressor genes can lead to the commencement and/or progression of carcinogenesis[16,17]. The elevation in copper concentrations may be due to the movement of copper from tissue to serum. Therefore, the present study evaluated the effect of chemoradiation on serum TAC, and MDA and copper concentrations in patients with CaCx.

Materials and Methods

The prospective study was conducted between November 2013 and November 2015. Fifty patients with histopathologically proven CaCx who visited the Department of Oncology & Gynaecology, at Vydehi Institute of Medical Sciences and Research Centre were recruited for the study. Subjects with any condition such as severe cardiovascular, respiratory diseases, diabetes mellitus, neurologic and psychiatric disorders, renal disorders and subjects on any medication such as oxidants vitamins, minerals, cigarette smokers, and alcoholics were excluded from the study.

Age-matched healthy women (n=50) visiting the hospital for a routine health check-up and hospital staff members willing to participate in the study were included as healthy controls. Informed consent was obtained and approximately 3 mL of blood was collected before and after treatment (chemoradiotherapy). Serum was separated from the blood and stored at -40 °C until required for analysis.

Chemotherapy was five cycles of cisplatin weekly in the dose of 40 g/m^2. Radiotherapy was brachytherapy with four fractions of 7 Gy each and two applications were one week apart.

In both groups, the TAC of serum was estimated using a FRAP assay (ferric reducing antioxidant power or the ferric reducing ability of plasma) according to the method of Benzie & Strain, 1996[18], MDA was measured using the method of Satoh[19], and copper was measured using a modified spectrophotometric micro-method with guanidine hydrochloride[20]. In addition, these parameters were estimated in patients with CaCx before and after chemoradiation.

Ethical clearance was obtained from the institutional ethical committee of our institution prior to starting the study (reference no: VIMS & RC/IEC/019/2013-14).

Statistical Analysis

The results were compiled in an excel spreadsheet, and frequency distribution and Bayesian analysis were performed using the SPSS v 16.0 software package (SPSS, Inc., Chicago, IL, USA).

Results

In this study, 50 healthy controls and 50 patients with CaCx who fulfilled the eligibility criteria were included in the analysis. The subjects included in the study were females within the age group of 25-65 years. The average age of presentation among the patients was 43.98±6.38 years (Table 1).

The mean serum copper concentration in the CaCx group and control group was 152.96±32.88 µg/dL and 104.88±24.45 µg/dL, respectively. The mean serum TAC in the CaCx group and control group was 781.36±228.88 µmol/L and 1088.94±185.07 µmol/L, respectively. The mean serum MDA concentration in the CaCx group and control group was 2.72±1.01 nmol/mL and 1.17±0.52 nmol/mL, respectively. These results indicated that serum copper and MDA concentrations were significantly (p<0.001) increased in patients with CaCx when compared with the controls, and serum TAC was significantly (p<0.001) decreased in the patient group compared with the controls (Figure 1).

Serum values of TAC, MDA, and copper before andafter chemoradiation were 777.9±227.8 µg/dL, 2.7±1.0 µg/dL, and 153.2±32.6 µg/dL, and 917.8±358.2 µg/dL, 2.5±0.92 µg/dL, and 153±33.7 µg/dL, respectively. Paired sample t-test analysis showed a significant increase and a decrease in TAC (p=0.018), and MDA (p<0.001), respectively, after chemoradiotherapy, whereas the changes in the concentrations of copper, were insignificant (p=0.405). There was a position correction of TAC with copper and MDA with copper (Figure 2).

Table 1. Age distribution of healthy controls and cervical cancer (CaCx) patients

Age (years)	Healthy controls (n=50)		Cervical cancer cases (n=50)	
	No	%	No	%
20-30	25	50	1	2
31-40	18	36	14	28
41-50	7	14	25	50
51-60	0	0	10	20
Mean ± SD	31.56±6.84		43.98±6.38	

SD: Standard deviation

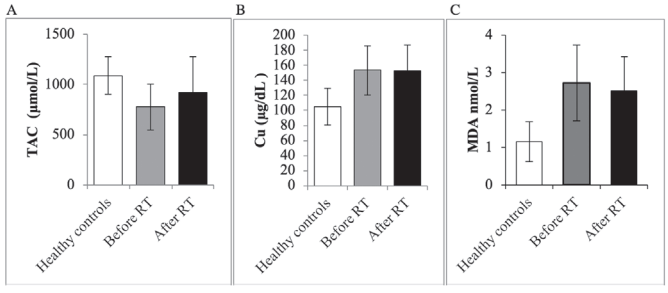

Figure 1. Serum total antioxidant capacity, malondialdehyde, and copper status of health controls and patients with cervical cancer before and after treatment

RT: Radiotherapy; data expressed as mean ± SD; **indicates p<0.001; *indicates p<0.05.

SD: Standard deviation, TAC: Total antioxidant capacity, MDA: Malondialdehyde, Cu: Copper

Discussion

Exposure of cells to chemotherapy or radiotherapy causes the generation of free radicals and intracellular ROS, which induce cancer cell death. The present study was devised to evaluate and compare the serum values of TAC, MDA, and copper in patients with confirmed CaCx and normal healthy female subjects. There was a negative correlation between serum copper with TAC, and serum TAC with MDA, and a positive correlation between serum copper and MDA.

The role of oxidative stress in the causation of CaCx has been studied extensively. Factors determining the development and progression of CaCx include an imbalance between the detrimental effects of oxidative stress and the antioxidant defense system of the body. In our study, serum copper concentrations were studied in patients with CaCx because copper acts both as pro-oxidant and antioxidant.

Copper in its free, unbound form catalyzes the production of various toxic free radicals[15]. Elevated copper concentrations have the potential to produce a relatively continuous supply of free radicals and ROS formed within cells are highly reactive and are able to oxidize most of the biomolecules within the cell, leading to tissue injury and cancer. ROS have been associated for many years with oncogenesis; however, recently a new role has emerged for ROS as mediators of signaling pathways, leading to cell proliferation and tumor initiation and promotion[21].

In our study, we obtained a significant (p<0.001) increase in serum copper concentrations in patients as compared with controls. Our results of high serum copper in patients with CaCx are also in agreement with several studies that found increased concentrations of serum copper in subjects with CaCx when compared with healthy controls[6,22-24]. Although, the cause of the increase in serum copper concentrations

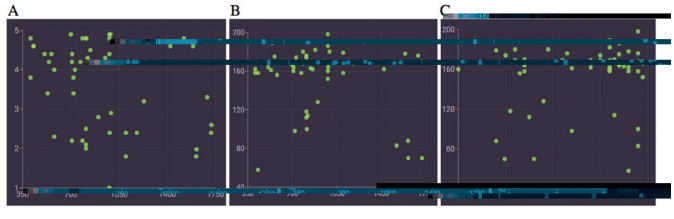

Figure 2. Correlation curve between: TAC-MDA (A), TAC-Cu (B), and MDA-Cu (C)

TAC: Total antioxidant capacity, MDA: Malondialdehyde, Cu: Copper

among patients with cancer is not known, it was proposed to be related with the increased liver production of copper-containing ceruloplasmin as an inflammatory response to cancer or from a tumor-induced decrease in the catabolism of the serum ceruloplasmin[22]. The meta-analysis by Zhang et al.,[23] showed significant evidence of higher serum copper concentrations in patients with CaCx than in controls, suggesting that serum copper exposure was a risk factor in CaCx. The increased copper level could be related to the fact that copper is needed to form new blood vessels and because cancer needs them in order to grow[25]. Hence, the increase in copper values in patients with CaCx.

The other finding of our study was a significant ($p<0.001$) decrease in serum TAC in patients as compared with controls. These results were in line with those of Demirci et al.,[26] and Rong et al.,[27] who reported the altered antioxidant status of patients with CaCx compared with healthy controls. However, Lee et al.,[28] stated that cervical intraepithelial neoplasia was also associated with lower blood antioxidant capacity levels. Kim et al.,[29] found that CIN was also associated with lower blood antioxidant capacity levels. The human body contains a complex antioxidant defense system that depends on the dietary intake of antioxidants as well as the endogenous production of anti-oxidative compounds such as glutathione[30].

Antioxidants are cytoprotective chemicals that prevent oxidative damage caused by free radicals. ROS and nitrogen species, which are oxygen and nitrogen-derived free radicals, are generated naturally as by-products of cellular metabolism[15]. Under physiologic conditions, free radicals are immediately rendered inactive by antioxidants. However, in oxidative stress, these free radicals remain in excess and cause damage by reacting with macromolecules such as nucleic acids, proteins, polyunsaturated fatty acids, and carbohydrates[30]. Oxidative damage has been associated with the pathogenesis of many chronic medical disorders viz. atherosclerosis, cancer, arthritis, and neurodegenerative disorders[31]. DNA damage and abnormal DNA repairs are prime factors in the causation of cancer. Hence, the association between a low antioxidant level and various malignant and premalignant conditions has been assessed by researchers.

Further, we showed a significant increase ($p<0.001$) in serum MDA concentrations in patients with CaCx. Grace et al.,[32] estimated MDA in patients with CaCx to assess the extent of lipid peroxidation and found similar results of increased circulating levels of MDA. They attributed it to an increase in oxidative stress due to a deficiency of antioxidant mechanism. They also observed an increase in lipid peroxidation and a decline in enzymatic antioxidant status in patients with CaCx. Naidu et al.,[6] also found increased levels of MDA and suggested that it was a possible cause in the progression of CaCx. The same results of elevated MDA concentrations were found by Demirci et al.,[26] in patients with CaCx when compared with a control group. As per Demirici et al.,[26] oxidative damage leads to the formation of products such as MDA, and DNA damage, which may, in turn, lead to mutagenesis, carcinogenesis, and cell death.

Study Limitations

There are some limitations in this study. This is a single centre hospital based study with small number of patients, the assessment of other oxidative enzymes, nutritional status are needed with larger patients size to get the solid evidence of antioxidants levels after receiveing the chemoradiotherapy.

Conclusion

The present findings demonstrate the imbalance in serum TCA, MDA, and copper among patients with CaCx when compared with healthy controls. These changes may play an important role in the pathogenesis and progression of CaCx through the involvement of these parameters in exaggerated oxidative stress. Further, chemoradiotherapy improved its anti-oxidant capacity. Extended studies are needed to evaluate the concurrent use of antioxidants with chemoradiotherapy for improving the disease prognosis.

Acknowledgment: We are thankful to the patients who gave their consent to conduct this study.

Ethics

Ethics Committee Approval: Ethical clearance was obtained from the institutional ethical committee of our institution prior to starting the study (reference no: VIMS & RC/IEC/019/2013-14).

Informed Consent: Informed consent was obtained.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: S.S., Design: S.S., Data Collection or Processing: S.S., Analysis or Interpretation: S.S., B.S.K., Literature Search: S.S., B.S.K., Writing: B.S.K.

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Case Report / Olgu Sunumu

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An overview of female genital mutilation

Kadın genital mutilasyonuna genel bir bakış

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Abstract

Female genital mutilation (FGM) includes procedures that intentionally alter or cause injury to the female genital organs for non-medical reasons. To present a case of type III FGM corrected by de-infibulation for treatment of sexual dysfunction. A 31-year-old woman who had FGM reporting unconsummated marriage presented to our clinic clinic. The patient had undergone type III FGM at age 7 in her country. Surgical correction was performed. By de-infibulation, the vaginal and urethral orifices were revealed after incision of scar tissue. The World Health Organization classifies FGM in four types. Type III FGM is narrowing of the vaginal orifice with the creation of a covering seal by cutting and appositioning the labia minora and/or the labia majora, with or without excision of the clitoris (infibulation). De-infibulation surgery is recommended for resolving problems related with sexual dysfunction and childbirth.

Keywords: Female genital mutilation, infibulation, sexual dysfunction

Öz

Kadın genital mutilasyonu (FGM), kadın dış genital organlarının tıbbi olmayan nedenlerle eksizyon yöntemi veya kadın genital organlarının yaralanmasına yol açan prosedürleri içerir. Seksüel disfonksiyonun tedavisi için de-infibulasyon cerrahisi yapılan tip III FGM olgusunu sunmaktır. FGM tanısı konan 31 yaşında kadın hasta cinsel ilişkiye girememe şikayeti ile kliniğe başvurdu. Kendi ülkesinde 7 yaşında tip III FGM uygulanan hastaya düzeltme cerrahisi yapıldı. De-infibulasyon cerrahisi ile skar dokusunun insizyonu sonrası vajinal ve üretral orifisler ortaya çıkarıldı. Dünya Sağlık Örgütü, FGM'yi dört tipte sınıflandırır: Tip III (infibulasyon) klitoris eksizyonu olsun olmasın labia minora ve/veya labia majusun kesilmesi ve mühürlemesi yoluyla vajinal orifisin daraltılması işlemidir. Seksüel disfonksiyon ve doğumla ilgili komplikasyonların çözümü için de-infibulasyon cerrahisi önerilir.

Anahtar Kelimeler: Kadın genital mutilasyonu, infibulasyon, seksüel disfonksiyon

Introduction

Female genital mutilation (FGM) includes procedures that intentionally alter or cause injury to the female genital organs for non-medical reasons. The practice, which is also known as female circumcision or female genital cutting, is typically performed by a traditional circumciser using a blade under unsafe conditions, mostly on young girls between infancy and age 15 years. The idea of performing the procedure by medical staff in order to make it safer is condemned because this procedure is internationally accepted as a violation of the human rights of girls and women[1,2]. More than 3 million girls are estimated to be at risk each year, and 200 million women living today in 30 countries have undergone the procedures[1]. The practice is most common in the western, eastern, and north-eastern regions of Africa, in some countries of the Middle East and Asia, as well as among migrants from these areas. There have been international efforts to persuade practitioners to abandon FGM, and it has been outlawed or restricted in most of the countries in which it occurs.

The procedures are mostly performed on young girls sometime between infancy and adolescence, and occasionally on adult women. The reasons why FGM is performed vary from one region to another. It is often considered as a necessary part

PRECIS: To identify the possible risk factors for postpartum urinary retention.

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of raising a girl, and a way to prepare her for adulthood and marriage. FGM is a social convention (social norm), there is social pressure to comply with the expectations of society, and the need to be accepted socially and the fear of being rejected by the community leads to FGM being performed in these countries. FGM is often motivated by beliefs about what is considered as acceptable sexual behavior[3].

Globalization and immigration has led to the recognition of this problem in countries where FGM is not practiced[4]. The European Institute of Gender Equality estimates that 180,000 women and girls are at risk for FGM each year in Europe.

World Health Organization (WHO) classifies this procedure in four types[4].

WHO classification of female genital mutilation

Type I (clitoridectomy): this is the partial or total removal of the clitoris (a small, sensitive and erectile part of the female genitals), and in very rare cases, only the prepuce (the fold of skin surrounding the clitoris).

Type II (excision): this is the partial or total removal of the clitoris and the labia minora, with or without excision of the labia majora.

Type III (infibulation): this is the narrowing of the vaginal opening through the creation of a covering seal. The seal is formed by cutting and repositioning the labia minora, or labia majora, sometimes through stitching, with or without removal of the clitoris (clitoridectomy).

Type IV: this includes all other harmful procedures to the female genitalia for non-medical purposes, e.g. pricking, piercing, incising, scraping, and cauterizing the genital area.

In some populations, infibulation, which involves cutting the labia and suturing the vulva leaving a small orifice for urination and menstruation, constitutes 15% of cases[5]. FGM in the short term may lead to severe complications such as pain, excessive bleeding (hemorrhage), genital tissue swelling, fever, infection, urinary problems (painful urination, urinary tract infections), vaginal problems (discharge, infections), menstrual problems (dysmenorrhea, hematocolpos), sexual and psychological problems, and difficulty in pregnancy and childbirth may arise after the procedure.

Long-term consequences include: urinary problems (painful urination, urinary tract infections; vaginal problems (discharge, itching, bacterial vaginosis and other infections), menstrual problems (e.g. painful menstruations, difficulty in passing menstrual blood), keloid formation on the scar tissue, sexual problems (e.g. pain during intercourse, decreased satisfaction), increased risk of childbirth complications (e.g. perineal tear, difficult or prolonged labor, increased rate of cesarean section and postpartum hemorrhage, increased need for newborn resuscitation), and rarely newborn deaths.

A need for later surgeries may arise due to FGM, especially with FGM procedures that seal or narrow the vaginal opening, which needs to be cut open later to allow for sexual intercourse and childbirth (de-infibulation). Sometimes genital tissue is stitched again several times (re-infibulation), especially after the delivery. Then the woman has to endure repeated opening and closing procedures and thus immediate and long-term risks, psychological problems (e.g. depression, anxiety, post-traumatic stress disorder, low self-esteem), and health complications of FGM are augmented[6].

A patient with type III FGM who presented to our clinic because of sexual dysfunction and underwent de-infibulation surgery is presented.

Case Report

Our patient was a 31-year-old, gravida 0 woman with regular menstrual cycles. She had been married for two weeks. She was admitted to our clinic because she was unable to have vaginal sexual intercourse. The patient had undergone genital mutilation at the age of 7 years in Somalia. A gynecologic examination revealed a totally excised labia majora and labia minora and clitoris, and a single orifice was observed in the perineum (Figure 1).

Detailed counselling was conducted by the gynecologist and a written signed consent was obtained that covered an explanation of the de-infibulation procedure, and the patient also gave consent for the publication of the case. The de-infibulation procedure was performed under anesthesia. The

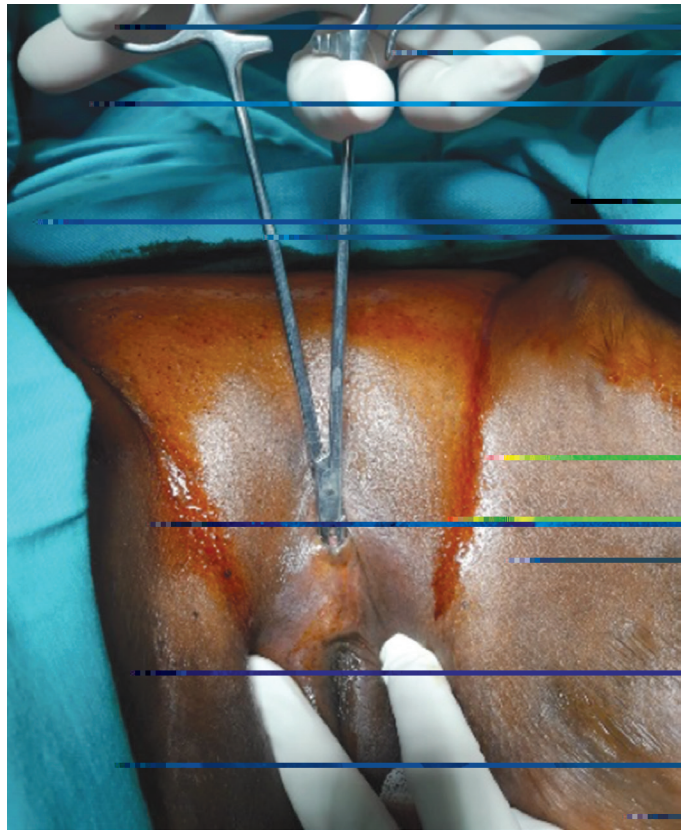

Figure 1. Insertion of Kelly clamp through the orifice and moved caudally in the tunnel-shaped space formed under the fusion line of the scar tissue

patient was prepared in the lithotomy position under sterile conditions. A Kelly clamp was gently inserted through the orifice and moved caudally into the tunnel-shaped space formed under the fusion line of the scar tissue. The scar tissue was then excised medially under the guidance of the Kelly clamp. The urethral orifice was observed at the upper part of the vaginal introitus and the hymenal membrane was found to be intact (Figure 2). The separated ends of the remains of the labia were repaired by suturing. Subsequently, bladder catheterization was performed in order to control the patency of the urethra, which showed a normal urethra (Figure 3). At the end of the procedure, a dressing with estriol cream and nitrofurazone was applied on the incision site in order to enhance epithelization. The patient had daily cleaning and dressing applications and was discharged uneventfully at day 3 postoperatively. The couple upon discharge was referred to the sexual dysfunction clinic of the hospital. During the 2-month follow-up after the surgery, the patient had a full recovery and was able to perform vaginal intercourse uneventfully.

Discussion

Girls ranging from newborn up to the adolescent period and rarely adult women are at risk for FGM in societies and communities where FGM is a tradition. Cultural and social reasons of FGM vary according to region. The reasons include: religion, fear of exclusion by society, protection of virginity before marriage, reduction of extramarital sexual unity, being seen as a part of the upbringing of girls or as a preparation for marriage and adulthood, perception of beauty and cleansing, and a necessity for being a woman.

For many years, international efforts have been made to ensure that those who practice FGM abandon this procedure[1]. As a result of these efforts, implementation is prohibited or restricted in most countries; however, these laws are not fully implemented. The short-term complications of FGM range from pain, infection, and bleeding to death due to these complications. HIV and tetanus infections are the most serious infections that might arise after FGM. These infections have a higher incidence in women with type II FGM[7]. Reyners et al.,[8] reported an estimated mortality of 1 in 500 circumcisions. In countries where FGM is not a tradition or a norm, acute complications of FGM can be very rarely seen, but medical workers may still encounter women with FGM-related long-term health problems ranging from urogenital disorders to sexual and mental health problems because of immigration from the countries where FGM is a well-accepted practice among the community members. Difficulty during the first vaginal penetration is very common

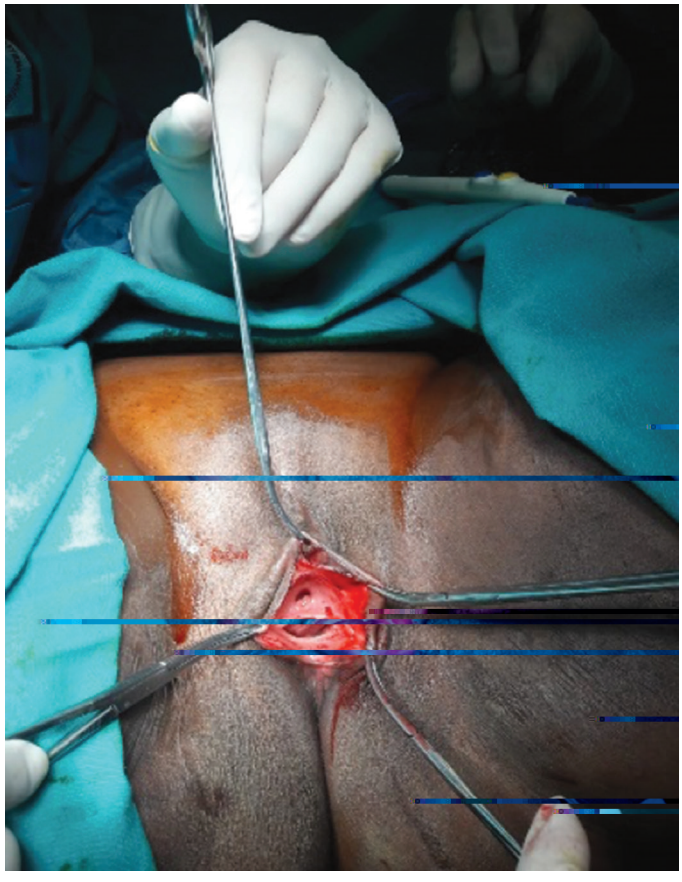

Figure 2. After the scar tissue was excised urethral orifice, vaginal introitus and an intact hymenal membrane were observed

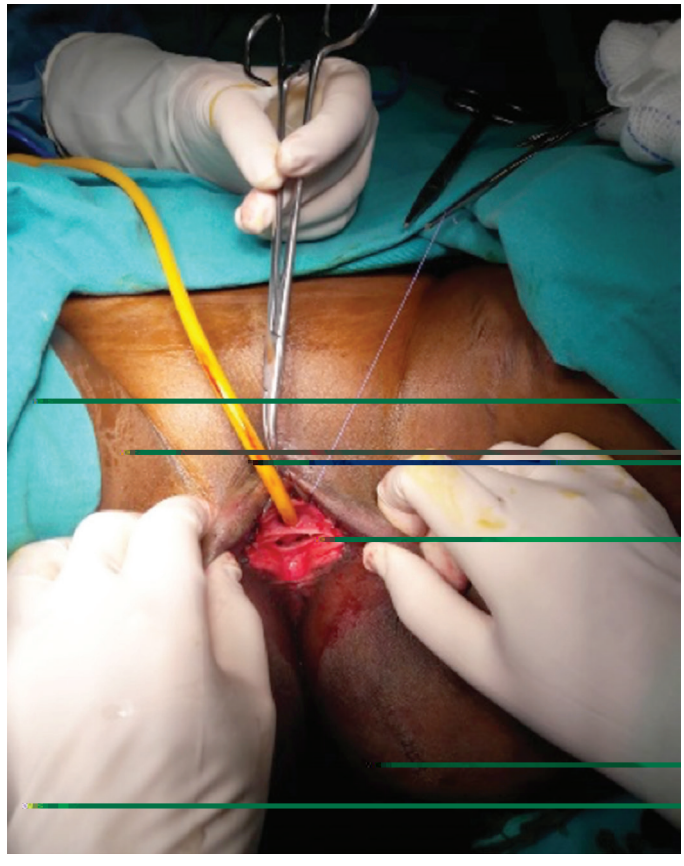

Figure 3. Restoration and visualization of the vaginal introitus and urethral orifice

especially in women with infibulation because the first vaginal sexual act results in pain and sometimes requires a surgical intervention or results in perineal tearing[9]. De-infibulation restores urinary and vaginal function, but these women need further counselling and support due to the psychological effects of this traumatizing experience[10,11].

Ethics

Informed Consent: written signed consent was obtained by patient.

Peer-reviewed: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical practices: B.D., Concept: B.D., Design: B.D., Data Collection and Processing: N.İ., S.A.T., Analysis and Interpretation: B.D., Literature Search: N.İ., S.A.T., Writing: B.D.

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

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Post-LSCS uterocutaneous fistula-utility of magnetic resonance imaging in its diagnosis

LSCS sonrası uterokütan fistül-tanısında manyetik rezonans görüntülemenin yararlılığı

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Abstract

The present report describes one of the rarest complications of cesarean section, uterocutaneous fistula, diagnosed on magnetic resonance imaging (MRI). A 37-year-old female with history of lower segment caesarean section (LSCS) four years previously presented with a chief symptom of discharge from the right end of a Pfannenstiel incision and on further evaluation was found to have uterocutaneous fistula arising from the LSCS scar to the right end of the abdominal incision. Uterocutaneous fistula is a rare delayed complication of LSCS and MRI plays a definitive role in the accurate diagnosis and delineation of the tract. The present case highlights that although rare, uterocutaneous fistulae must be kept in mind in patients presenting with discharge from the abdominal incision site and MRI evaluation should be performed in such cases for appropriate delineation of the tract.

Keywords: LSCS, uterocutaneous fistula, MRI

Öz

Bu çalışmada; manyetik rezonans görüntüleme (MRG) ile tanısı konan ve sezaryen doğumun en nadir komplikasyonlarda biri olan uterokütan fistülün tanımlanması amaçlanmıştır. Dört yıl önce alt segment sezaryen öyküsü (LSCS) olan 37 yaşındaki kadın hasta, pfannenstiel insizyonunun sağ ucundan akıntı şikayeti ile başvurdu ve daha ileri değerlendirmelerde LSCS skarından abdominal insizyonun sağ ucuna kadar uterokütan fistülün olduğu tespit edildi. Uterokutanöz fistül, LSCS'nin nadir görülen gecikmiş bir komplikasyonudur ve MRG, alanın tam tanısında ve tasvir edilmesinde belirgin rol oynamaktadır. Buradaki olgu, abdominal insizyon bölgesinde akıntı nedeni ile başvuran hastalarda nadir olmasına rağmen, uterokutanöz fistülün akılda tutulması gerektiğini ve bu gibi durumlarda alanın uygun şekilde tasvir edilmesi için MRG değerlendirmesinin yapılması gerektiğini vurgulamaktadır.

Anahtar Kelimeler: LSCS, uterokütan fistül, MRG

Introduction

Uterine fistulae usually occur between the uterus and bowel or bladder (uterocolic or uterovesical) with uterocutaneous forming the rarest variety of uterine fistulae. The fistulae occur due to postoperative injuries or infections, use of drains, and incomplete closure of incision[(1)]. Uterocutaneous fistulae, being a rare condition, need appropriate diagnosis for which magnetic resonance imaging (MRI) plays the most important role, thereby helping in the proper delineation of the tract to guide the appropriate management[(2)]. The most common cause of uterocutaneous fistula is incomplete closure of the cesarean section wound. Earlier diagnosis can be made using fluoroscopic or cross-sectional modalities[(3)]. Surgical repair is the treatment of choice with preoperative gonadotropin administration showing better outcomes, but few cases may result in hysterectomy[(3)]. We describe this

PRECIS: To identify the possible risk factors for postpartum urinary retention.

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case of uterocutaneous fistula, which occurred 4 years after a caesarean section and was diagnosed using MRI.

Case Report

A 37-year old female with a history of lower segment cesarian section (LSCS) performed four years previously presented with the chief symptom of discharge from the incision site. MRI of the pelvis was performed, which revealed an enhancing fistulous tract originating from the site of the lower segment of the cesarean section and traversing through the parietal wall opening at the right edge of abdominal incision scar (Figure 1). The diagnosis of uterocutaneous fistula following LSCS was formulated. After exploratory laparotomy, excision of the tract was performed followed by administration of broad-spectrum antibiotics with postoperative imaging showing no active tract (Figure 2). The patient remains under follow-up and is currently free of symptoms.

Discussion

During the era of classic cesarean section, a number of cases of uterocutaneous fistula were reported but with the advent of LSCS, the frequency has decreased to a large extent. Most uterocutaneous fistulae owe their origin to infections (e.g. genital tuberculosis) complicating uterine or abdominal scars. Besides LSCS, the causes of uterocutaneous fistulae include post septic abortion, placement of drain, missed uterine perforation following a diagnostic laparoscopy[4,5].

Cases of post-partum hemorrhage wherein B-lynch sutures are placed have high risk of scar dehiscence, which may result in uterocutaneous fistula[6,7]. Other rare causes that may result in the formation of uterocutaneous fistula are patients with multiple abdominal myomectomies, history of hysterectomy, and as a primary presentation in underlying gynecologic malignancy such as endometrioid adenocarcinoma, which can predispose the weak cesarean scar to fistula formation[6-8]. The blood leakage from the incision site during menstruation has been described as pathognomonic of the uterocutaneous fistula[9].

The various modalities that can be used in the diagnosis of uterocutaneous fistula include fistulography with injection of contrast through the skin site, hysterosalpingography with injection of contrast via cervix, computed tomography (CT) scanning, and MRI. Fistulography and hysterosalpingography define the fistulous tract but cannot provide details of its communication with the other intra-abdominal viscera[1,3]. CT imaging helps in the proper delineation of the tract after the injection of the contrast agent through the abdominal site, but soft tissue resolution of CT scans is less compared with MRI[10,11]. MRI provides good soft tissue resolution, avoids radiation (as all other investigations involve significant radiation doses), and helps in proper delineation of the fistulous tract and its relation to the surrounding viscera. The assessment of other pelvic organs with greater spatial resolution is possible. Intravenous contrast administration shows the enhancement of the granulation tissue along the fistulous tract, which gives a clue about the active status of the fistula. Further, contrast agent can also be administered via the abdominal site as in other investigations to check the patency of the[12].

Hence, MRI forms the best investigative modality in the assessment of uterocutaneous fistulae and other pelvic post-operative complications.

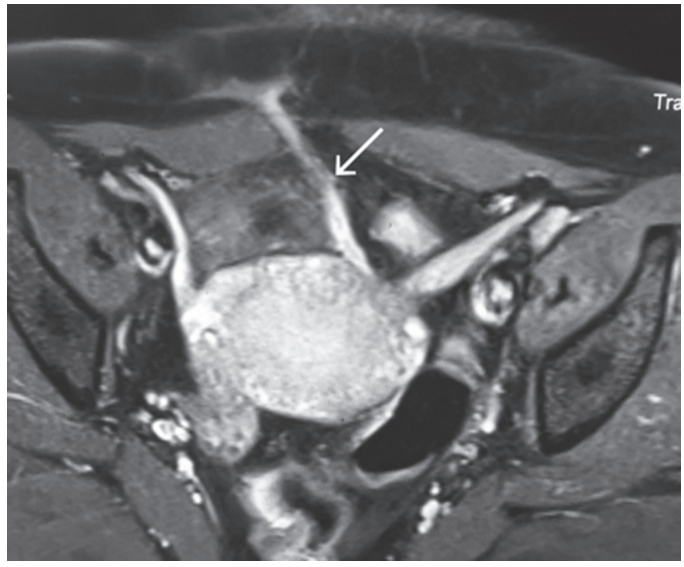

Figure 1. Post-contrast magnetic resonance image showing the enhancing fistulous tract (arrow) from the right end of the abdominal incision traversing through the abdominal cavity to the uterine wall

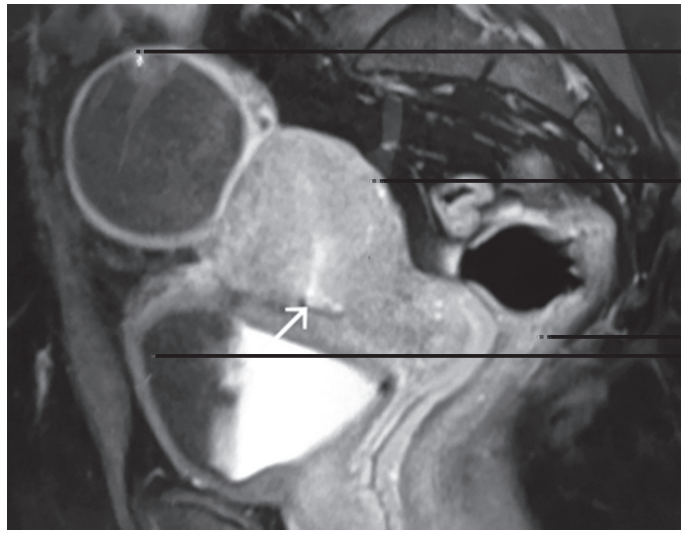

Figure 2. Post-surgical magnetic resonance image after 2 months, showing the LSCS scar (arrow) with no tract demonstrable. Additionally, she developed a simple ovarian cyst, which resolved on its own in 8 weeks

LSCS: Lower segment cesarian section

Ethics

Informed Consent: Written and informed consent form was obtained from patient for possible publication of these images and the case details.
Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Concept: T.G., Design: T.G., Data Collection or Processing: T.G., Analysis or Interpretation: F.S., O.A.S., Literature Search: F.S, O.A.S., M.A.D., Writing: M.I., I.K.
Financial Disclosure: Nil.
Disclosure of Interests: There are no financial, personal, political, intellectual or religious interests.

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Rupture of cerebral aneurysm during pregnancy: a case report

Gebelikte serebral anevrizma rüptürü: olgu sunumu

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Abstract

The most common cause of subarachnoid hemorrhage at the period of pregnancy and during puerperium is rupture of an intracranial aneurysm. It is five times more common in pregnant women than in non-pregnant women. This pathology is more common in primiparous women and in the third trimester of pregnancy. A 37-year-old woman who was admitted to the emergency department with sudden-onset headache and loss of consciousness was diagnosed with intracranial hemorrhage due to middle cerebral artery aneurysm rupture. The patient, who gave birth with emergency cesarean delivery, underwent surgery for subarachnoid hemorrhage. The case is presented here because of its rarity.

Keywords: Intracranial aneurysm, subarachnoid hemorrhage, pregnancy, puerperium, mortality

Öz

Hamilelik döneminde ve puerperium boyunca subaraknoid kanamanın en sık nedeni intrakraniyal anevrizma rüptürüdür. Gebe kadınlarda gebe olmayan kadınlara göre beş kat daha sık görülür. Primipar gebelerde ve gebeliğin 3. trimesterinde görülme oranı daha yüksektir. Ani başlayan baş ağrısı ve bilinç kaybı ile acil servise başvuran 37 yaşında, 34 haftalık gebeye orta serebral arter anevrizması rüptürüne bağlı intrakraniyal kanama tanısı konuldu. Acil sezaryen ile doğum yaptırılan hasta subaraknoid kanama nedeniyle opere edilmiştir. Hasta nadir görülen bir olgu olması nedeniyle sunulmuştur.

Anahtar Kelimeler: İntrakraniyal anevrizma, subaraknoid kanama, gebelik, puerperium, mortalite

Introduction

The incidence of intracranial bleeding from cerebral aneurysm rupture in pregnancy is rare[1,2]. On the other hand, rupture of an intracranial aneurysm still remains the most common cause of subarachnoid hemorrhage (SAH) during pregnancy and puerperium[3]. Its prevalence is five times higher in pregnant women than in non-pregnant women[4]. The incidence of SAH tends to increase during pregnancy and there is a need for more publications to document the risk.[2] SAH is the only paralysis species with female dominance, suggesting that reproductive factors may play a role in etiology[5]. It occurs more frequently in primiparous women and in the last trimester of pregnancy. Early menarche and nulligravida were found to increase SAH risk[6]. The mortality rate of maternal death due to the aneurysmal rupture is as high as 5 to 12%. In particular, the rupture of an intracranial aneurysm during pregnancy can lead to a fatal outcome in the mother and the fetus[1].

Herein, we report a 37-year-old woman who was admitted with sudden-onset headache and loss of consciousness. She was diagnosed as having intracranial hemorrhage from a rupture of middle cerebral artery (MCA) aneurysm.

Case Report

A 37-year-old woman was admitted to the emergency department with sudden-onset severe headache, vomiting, and loss of consciousness. She was unconscious and intubated at admission. The Glasgow Coma Scale (GCS) was detected as 5 eye response (E): 1, verbal response (V): 1, and motor response (M): 3 in a neurologic examination. Light reflex could not be taken bilaterally and pupils were miotic. Flexion response to painful stimuli was obtained. It was determined that the patient was pregnant at admission. The patient who was G7 P4 A0 D&C 2 had not received any obstetric care during pregnancy. A single live fetus compatible with 34

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weeks' gestation and oligohydramnios was found. A vaginal examination revealed a multipara dilatation and no active vaginal bleeding. Her blood pressure was 120/70 mm Hg. The complete blood count and biochemical parameters were found within normal limits. Cranial computed tomography (CT) and CT angiography were decided to perform as a result of neurology and neurosurgery consultations. Cranial CT and CT angiography were performed with protection of the abdomen. A hematoma was detected in the left Sylvian fissure. Additionally, there was hemorrhage in all ventricles, which was compatible with stage IV SAH according to the classification of Fisher (Figure 1). The Yasargil classification was compatible with grade IV.

After the evaluation of the clinical status of the mother, a cesarean delivery was decided. The cesarean section procedure was performed under emergency conditions and a 2520 g live male baby with a 9-10 Apgar score was delivered. External ventricular drainage was performed from the right Kocher point by a neurosurgery team for the SAH of the patient immediately after the cesarean delivery. The mean arterial structures and Sylvian fissure were reached with an approach from the left side. A ruptured aneurysm with active bleeding was seen in the left MCA tract, which was clipped. The patient was taken to the intensive care unit after the operation. The clips were checked in follow-up cranial tomography (Figure 2). Unfortunately, the patient died four days after the operation.

Discussion

Maternal mortality is a challenge for obstetric physicians, and it is unacceptably high. The maternal mortality rate was 216 per 100,000 live births with a 43.9% reduction worldwide in 2015 when compared with the results of 1990[7]. However, it was 13.7 per 100,000 live births in Turkey in 2015[8]. The ratio of SAH-related maternal death to all maternal deaths was 2.8% in a study based on autopsy results[9]. While evaluating this ratio, it should be kept in mind that the autopsy rate in maternal deaths is very low. In another review, it has been found that the death rate of patients who were diagnosed as having aneurysmal SAH during pregnancy was 1/10[10].

Aneurysms in pregnancy occur after 30 years of age and commonly rupture in the last trimester[11,12]. The distribution rates of intracranial aneurysms diagnosed in the first, second or third trimester in pregnancy are 6%, 31%, and 55%, respectively, and the incidence of the puerperal period is 8%. In our case, the patient was aged 37 years and in her third trimester of pregnancy. More than one aneurysm can be found in 20% of cases[13]. Hormonal changes and hemodynamic stress may cause an increase in the risk of aneurysm development and rupture during pregnancy. Such changes are mostly seen in the last three months of pregnancy and the process of labor[14]. The physiologic effects of pregnancy can cause water retention in the body. This causes cardiac output and blood volume increase and ultimate changes in vascular layers[15].

A differential diagnosis is necessary in cases of neurologic deficit including sudden acute headache and decreased consciousness. Eclampsia, pituitary apoplexy, intra-arterial occlusions, dural sinus thrombosis, intracranial space-occupying lesions, meningitis, encephalitis, and demyelinating diseases should be considered in the differential diagnosis[2]. Eclampsia is the most common disease in the differential diagnosis of SAH because of the similarity of the presenting symptoms such as acute-onset high blood pressure, seizures, and decreased consciousness. Lumbar puncture, CT, and MRI can be considered as diagnostic tools[1]. The diagnosis is made with neuroimaging (CT, MRI, and cerebral angiography). Although CT scanning exposes the fetus to radiation, this radiation exposure can be disregarded because the diagnosis is more important. For this reason, the evaluation of a pregnant patient arriving with headache requires detailed neurologic evaluation. Lumbar puncture should be performed if clinical suspicion persists, even if CT and MRIs are negative[16]. The clinical symptoms and signs in our patient were highly suggestive of the presence of a cranial pathology. Accordingly, we performed brain CT and showed the presence of a SAH, after which we performed CT angiography.

In patients who do not receive treatment, the probability of recurrent hemorrhage is 33-50% and maternal mortality rates

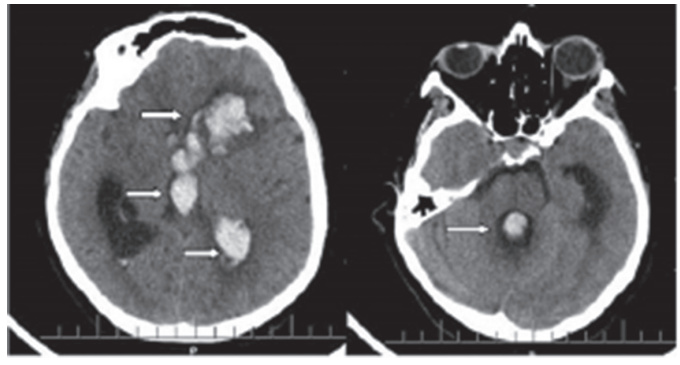

Figure 1. The patients preoperative axial brain computed tomography showing hemorrhage in the left lateral, third, and fourth ventricles, and parenchyma

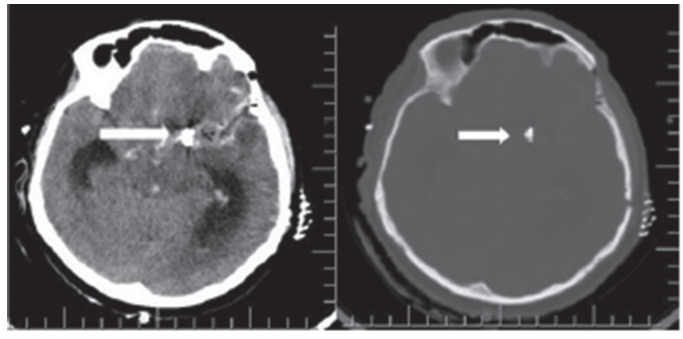

Figure 2. The patients preoperative axial brain computed tomography showing aneurysm clips

are about 50% to 68%[2,13]. The fetal mortality rates are lower in surgical patients than in pharmacologically treated only patients[17]. Therefore, surgical treatment should be made as soon as possible[11,12].

The management of SAH from aneurysmal rupture should be multidisciplinary in pregnant women. It is very important that the consultation of neurosurgery be provided as soon as possible. The neurology consultation may predict fetal and maternal outcomes or direct treatment. The GCS has been shown to correlate significantly with fetal and maternal outcomes[10]. The GCS was 5 in our case, which may be accepted as a bad-prognosis indicator. SAH management in pregnancy can be evaluated in two parts. In the early pregnancy period, the treatment is the same as with non-pregnant patients. In other periods of pregnancy, emergency cesarean section should be performed before SAH treatment[18]. In early pregnancy cases when the aneurysm is clipped, pregnancy can progress until term resulting in vaginal birth[19]. Cesarean section should be performed in several circumstances such as severity of the mother's clinical state (coma, brainstem damage) and in an aneurysm diagnosed at the term of pregnancy[20].

Aneurysmal SAH clipping is recommended in the treatment. In a case series, it was assessed that intravascular embolization was performed in all cases except one; the reason for treating with surgery was the presence of severe vasospasm. Several studies in recent years demonstrated the efficacy and safety of endovascular coiling in the treatment of cerebral aneurysms[21].

There are many factors affecting the treatment of ruptured intracerebral aneurysms, such as the type, size, and site of the aneurysm. Microsurgical clipping or endovascular embolization can be applied, but surgical clipping is still the most used technique, obtaining excellent aneurysm occlusion and allowing the removal of blood and clots from the brain cisterns, despite the high post-surgery mortality and difficult dilatation of the vertebrobasilar system. Despite a few negative cases reported in the literature, embolization is expected to become widespread. In both techniques, general anesthesia is used and the correlated risk between both techniques is similar[22].

If the patient is stable and close to term, vaginal delivery should be preferred. Cesarean section is more frequently used in cases of unruptured aneurysm, meningeal hemorrhage during labor, and if the patient's clinical and neurologic status is unfavorable[12]. If the intracranial aneurysm occlusion is performed before the delivery, delivery may occur by the vaginal route without any risk of recurrent bleeding. Although there is no evidence that the cesarean section is safer for either the mother or the fetus, it is frequently preferred because of its quickness and ease of monitoring[14]. Additionally, it is also possible to perform aneurysmal clipping immediately after the cesarean section[11]. In our case, cesarean section was performed, after which the ruptured aneurysms were clipped promptly after diagnosis.

Conclusion

In conclusion, rupture of cerebral aneurysm is still fatal during pregnancy in spite of the presence of all needed factors. We wanted to emphasize that, this phenomenon, in terms of sudden headaches and loss of consciousness, should remind us of other pathologies seen during pregnancy.

Ethics

Informed Consent: Written informed consent was obtained from the husband of patient.

Peer-reviewed: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.O., Ö.Ş.T., İ.S.D., Concept: T.O., İ.S.D., Design: M.K, Ö.Ş.T., Data Collection or Processing: T.O., Ö.Ş.T., Analysis or Interpretation: T.O., M.K., Literature Search: Ö.Ş.T., T.O., Writing: T.O., M.K.

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

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Case Report / Olgu Sunumu

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Asymptomatic microperforated transverse vaginal septum presenting with primary infertility: a rare form of mullerian anomaly

Primer infertilite ile başvuran asemptomatik olguda perfore transvers vajinal septum rezeksiyonu: nadir görülen bir müllerian anomali formu

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Abstract

Transverse vaginal septum is a rare type of mullerian anomaly resulting from failure of the canalization of the vaginal plate at the point where the urogenital sinus meets the mullerian duct and usually presents at menarche with symptoms of outflow tract obstruction. Instead, patients with a perforated septum often have normal menses and usually present with difficulties with intercourse or infertility. A 24-year-old patient with 5 years of infertility is reported. Following assessment, isolated microperforated transverse vaginal septum (U0C0V3 according to the new classification system of the European Society of Human Reproduction and Embryology/European Society for Gynaecological Endoscopy for congenital uterine anomalies) was detected with no additional urogenital anomaly and simple excision of the septum and end-to-end vaginal anastomosis was performed. The patient became pregnant spontaneously 2 months after the operation when sexual intercourse was permitted. Transverse vaginal septum, which presented itself with no clinical findings and only primary infertility, is discussed with a review of the existing literature.

Keywords: Transverse vaginal septum, infertility, congenital malformation

Öz

Transvers vajinal septum, müllerian anomalilerin nadir görülen bir türüdür ve ürogenital sinüsün müllerian kanal ile birleştiği noktada vajinal plağın kanalizasyonda başarısızlıktan kaynaklandığı düşünülmektedir. İmperfore septumlar genelde erken adölesan dönemde menstrüasyonun obstrüksiyonu sonrası hematokolpos, hematometra ile görülür. Perfore septumu olan hastalarda ise menstrual siklus normaldir ve bu hastalar kliniğe cinsel ilişki sırasında zorlanma ve infertilite ile başvururlar. Bu çalışmada 5 yıldır korunmasız cinsel ilişkiye rağmen gebe kalamayan 24 yaşındaki bir primer infertil olgu sunulmuştur. Yapılan değerlendirme sonucunda izole mikroperfore transvers vajinal septum (konjenital uterin anomaliler için yeni European Society of Human Reproduction and Embryology/European Society for Gynaecological Endoscopy sınıflamasına göre U0C0V3) saptanmış, herhangi bir ek ürogenital anomali izlenmemiş ve septumun cerrahi eksizyonu sonrası uç uca anastomoz uygulanmıştır. Hastada operasyondan 2 ay sonra spontan gebelik izlenmiştir. Primer infertilite dışında hiçbir klinik bulgu vermeyen transvers vajinal septum olgusu bu çalışmada literatür taraması ile birlikte sunulmuştur.

Anahtar Kelimeler: Transvers vajinal septum, infertilite, konjenital malformasyon

Introduction

Transverse vaginal septum is a rare type of mullerian anomaly resulting from failure of the canalization of the vaginal plate at the point where the urogenital sinus meets the mullerian duct. Its incidence is estimated as 1/70,000 females, making it one of the rarest anomalies of the female genital tract[(1)]. Imperforate septum usually present early in adolescence with obstructed menstruation. However, patients with perforate septum often have normal menses and usually present with difficulties with intercourse or infertility. The exact localization and the thickness of the septa vary, but are more frequent in the upper vagina and mostly less than 1

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cm in thickness[2]. In this article, we present a patient with a perforated transverse septum who presented with primary infertility and underwent treatment of the septum.

Case Report

A 24-year-old patient with 5 years' infertility was admitted to outpatient clinic for treatment. She had no systematic disease. Her menarche started when she was aged 12 years and her menstrual cycle was regular. The patient did not describe any symptoms such as dysmenorrhea, pelvic pain or dyspareunia, nor did she have problems during sexual intercourse. Secondary sex characters were found to be compatible with her age. There was no pathology in the external genitalia. On speculum and digital examinations, a blind-ending vagina was detected. There was no orifice and the cervix was not visible. Transvaginal ultrasound revealed normal uterine and adnexal anatomy. Hematocolpos and hematometra were not detected. Therefore, a microperforated transverse vaginal septum was suspected. There were no other associated urogenital congenital anomalies of the upper and lower abdomen on ultrasound. In order to confirm the diagnosis, abdominopelvic magnetic resonance imaging (MRI) was performed following ultrasound gel injection into the proximal vagina, which showed a transverse vaginal septum at the middle part of the vagina, 23-mm distant from the introitus. The distance between the anterior fornix in the superior and this level of septum was 41 mm (Figure 1).

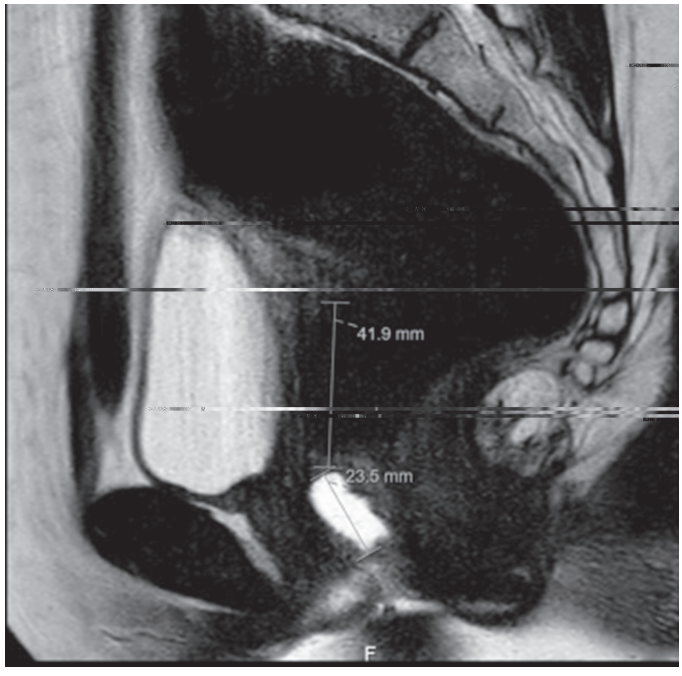

Figure 1. Sagittal view of the magnetic resonance imaging scan after gel injection into the vagina showing the exact level of the septum

(A: distance from introitus to septum: 23.5 mm; B: distance from septum to posterior vaginal fornix: 41.9 mm)

During surgery, transverse vaginal septum was excised circularly, and the proximal and distal parts were anastomosed. A normal-appearing cervical ostium was then visible. The vaginal tissue around the fibrotic tissues was sutured in a purse string fashion with late absorbable sutures. Diagnostic hysteroscopy and laparoscopy were also performed for the investigation of infertility. On hysteroscopy, a normal endometrial cavity with two normal tubal ostial orifices and a normal endocervical canal were seen. Laparoscopy also revealed normal pelvic anatomy and a methylene blue dye test showed bilateral patent tubes.

After the operation, to prevent vaginal stricture the patient wore a vaginal mold prepared with a sterile condom filled with tampons. This mold was changed every two days and repeated 5 times totally. Prophylactic antibiotics were given to prevent vaginal infection. Upon follow up, no vaginal infections, strictures or any gynecologic pathologies developed in the postoperative period. Wound healing was complete and sexual intercourse was permitted 8 weeks after the operation. She became pregnant spontaneously the next month and had 21 weeks of normal pregnancy at the time of writing this article.

Discussion

One of the rare causes of primary infertility is transverse vaginal septum. It results from either incomplete canalization of the vaginal plate or failure of the paramesonephric ducts to meet the urogenital sinus[2]. There are few data available in the literature about the classification or the surgical management of transverse vaginal septae. Additionally, the short or long-term results following surgical treatment are also not very clear[3].

The classification is made using the new European Society of Human Reproduction and Embryology/European Society for Gynaecological Endoscopy consensus in 2013 and transverse vaginal septum was accepted as the V3 subgroup among the mullerian duct anomalies[4]. Our case was classified as U0C0V3 because our patient had no associated uterine or cervical anomalies.

Perforated-type transverse vaginal septa is usually asymptomatic until adolescence or adulthood because these patients have no outflow obstruction. As in our case, they may present with infertility or sometimes with coital problems[5]. They may also be diagnosed incidentally during vaginal examination. The reason for infertility is not exactly clear, but microperforated septum may be an obstacle for the passage of sperm. Clinical examination, ultrasound, and MRI may all be used in the diagnosis and preoperative planning. Treatment involves surgical resection of the septum and anastomosis of the proximal and distal parts. The main goal during surgery must be to maintain the continuity of the vaginal epithelium and restoration of normal vaginal caliber and length.

Transverse septums can be seen at different locations of the

vagina. According to the study of Williams et al.,[6] 15-72% of the transverse vaginal septum cases are seen at the distal end of the vagina, 22-40% are seen at the mid-vagina, and 6-45% are seen at the proximal part. Our patient had a mid-vaginal septum. Diagnosis and the treatment plan should be made after performing a clinical examination, ultrasonography, and MRI. The treatment can be made with vaginal, laparoscopic, and abdominoperineal approaches according to the localization and the thickness of the septum. Complication rates are low if the septum is located at the distal part of the vagina and it is a thin, perforated septum. If the septum is at the mid-upper part of the vagina and it is not thicker than 2 cm, laparoscopy would be the correct treatment approach. If the septum is thicker than 2 cm, the abdominoperineal approach is necessary; however, complication rates are high[7]. These complications are mostly vaginal stenosis and reobstruction. In the study of Joki-Erkkilä and Heinonen[7] two of three patients with isolated transverse septae had reobstruction and needed reoperation despite their septal thicknesses being less than 1 cm. Therefore, to prevent such obstruction, regular postoperative dilator therapy is essential. Additionally, early coitus after complete healing must also be advised. We also performed diagnostic laparoscopy and hysteroscopy after excision of the septa, which showed an anatomically normal uterus, ovaries, and patent tubes, and also a normal endometrial cavity. Laparoscopy could have been skipped because we performed an MRI scan before the operation and it showed normal findings; however, we performed a laparoscopy to document tubal patency and to rule out endometriosis.

Conclusion

Transverse vaginal septum is a rare mullerian tract anomaly and selected patients can be treated by simple excision and anastomosing the proximal and distal vaginal tissue. It is safe, effective, and easy to perform. The recurrence and complication rates vary due to the location and the thickness of the septum. Surgical resection of the septum results in successful restoration of the genital tract anatomy and allows normal fertility.

Ethics

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.D., O.Y., C.A., S.Ö., Concept: E.D., O.Y., C.A., S.Ö., Design: E.D., O.Y., C.A., S.Ö., Data Collection or Processing: E.D., O.Y., C.A., S.Ö., Analysis or Interpretation: E.D., O.Y., C.A., S.Ö., Literature Search: E.D., O.Y., C.A., S.Ö., Writing: E.D., O.Y., C.A., S.Ö.

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