ISSN 1309-0399 • E-ISSN 1309-0380

JTGGA is now indexed in PubMed

TURKISH-GERMAN GYNECOLOGICAL EDUCATION and RESEARCH FOUNDATION

Journal of the Turkish-German Gynecological Association

Volume 15
Issue 3
September
2014

Cover Picture: Hassa et al. A metaphase II oocyte with perivitelline space

Original Investigations

AVES

Official Journal of the
Turkish-German Gynecological Education and Research Foundation
www.tajev.org

Official Journal of the
Turkish-German Gynecological Association
www.dtgg.de

www.jtgga.org

Journal of the
Turkish-German
Gynecological Association

Journal of the
Turkish-German Gynecological Association

Editorial Office

Address: Abdi İpekçi Cad. 2/7 34367 Nişantaşı, İstanbul-Turkey
Phone: +90 212 241 45 45 Fax: +90 212 241 44 08
E-mail: tajev@tajev.org

Owner and Responsible Manager
M. Cihat Ünlü

Official Journal of the Turkish-German Gynecological Education and Research Foundation
www.tajev.org

Turkish-German Gynecological Association
www.dtgg.de

Publisher
İbrahim KARA

Publication Director
Ali ŞAHİN

Deputy Publication Directors
Gökhan ÇİMEN
Ayşegül BOYALI

Publication Coordinators
Merve AKDEMİR SAĞLIK
Leda BAŞGÜL
Esra GÖRGÜLÜ
Ebru MUTLU

Sales Coordinator
Sinan Gökbörü BÜNCÜ

Finance and Administration
Veysel KARA

Project Assistants
Hakan ERTEN
Zeynep YAKIŞIRER
Betül ÇİMEN

Graphics Department
Ünal ÖZER
Neslihan YAMAN
Merve KURT

Contact:
Address: Büyükdere Cad. 105/9
34394 Mecidiyeköy, Şişli, İstanbul, TURKEY
Phone: +90 212 217 17 00
Fax: +90 212 217 22 92
E-mail: info@avesyayincilik.com

Yayın Türü: Yerel Süreli
Basım Tarihi: Eylül 2014
Basım Yeri: ADA Ofset Matbaacılık Tic. Ltd. Şti., Litros Yolu, 2. Matbaacılar S. E Blok, No: (ZE2) 1. Kat Topkapı, İstanbul, Türkiye
Telefon: +90 212 567 12 42

Journal of the
Turkish-German
Gynecological Association

Aims and Scope

Journal of the Turkish-German Gynecological Association is the official, open access publication of the Turkish-German Gynecological Education and Research Foundation and Turkish-German Gynecological Association and is published quarterly on March, June, September and December.

The target audience of Journal of the Turkish-German Gynecological Association includes gynaecologists and primary care physicians interested in gynecology practice. It publishes original work on all aspects of gynecology. The aim of Journal of the Turkish-German Gynecological Association is to publish high quality original research articles. In addition to research articles, reviews, editorials, letters to the editor and case presentations are also published.

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

Journal of the Turkish-German Gynecological Association is indexed in PubMed Central, EMBASE, Scopus, CINAHL, Gale/Cengage Learning, EBSCO, DOAJ, ProQuest, Index Copernicus, Tübitak/Ulakbim Turkish Medical Database and Turkiye Citation Index.

Subscription Information
Journal of the Turkish-German Gynecological Association is distributed free of charge to all physicians, specialists in gynecology field. For subscription please contact Turkish-German Gynecological Education and Research Foundation at www.jtgga.org. The access to tables of contents, abstracts and full texts of all articles published since 2000 are free to all readers via the journal's webpage. Visit the journal's home pages for details of the aims and scope and instruction to authors.

Permission
Permission requests to reproduce copies of articles for non-commercial use may be obtained from the Editorial Office:

Editor: Cihat Ünlü, M.D.
Address: Abdi İpekçi Cad. 2/7 34367 Nişantaşı-İstanbul-Turkey
Phone: +90 212 241 45 45
Fax: +90 212 241 44 08
E-mail: tajev@tajev.org

Advertising
Enquiries concerning advertisements should be addressed to Editorial Office:

Editor: Cihat Ünlü, M.D.
Address: Abdi İpekçi Cad. 2/7 34367 Nişantaşı-İstanbul-Turkey
Phone: +90 212 241 45 45
Fax: +90 212 241 44 08
E-mail: tajev@tajev.org

Instructions for Authors
Instructions for authors page at the journal is available in the journal content and at www.jtgga.org.

Disclaimer
The statements and opinions contained in the articles of the Journal of the Turkish-German Gynecological Association are solely those of the individual authors and contributors not of the Turkish-German Gynecological Education and Research Foundation, Turkish-German Gynecological Association, Turkish Society of Reproductive Medicine, Editorial Board or AVES.

The journal is printed on acid-free paper.

Journal of the
Turkish-German
Gynecological Association

Instructions for Authors

The "Journal of the Turkish German Gynecological Association" (ISSN 1309-0399; Abbreviated as "J Turk Ger Gynecol Assoc") is the official, open access publication of the Turkish-German Gynecological Education and Research Foundation and the Turkish-German Gynecological Association. Formerly named "ARTEMIS", the journal is published quarterly (March, June, September, December) in English and publishes original peer-reviewed articles, reviews, case reports and commentaries in the fields of Gynecology, Gynecologic Oncology, Endocrinology & Reproductive Medicine and Obstetrics. Reviews will be considered for publication only if they are prepared by authors who have at least three published manuscripts in international peer reviewed journals and these studies should be cited in the review. Otherwise only invited reviews will be considered for peer review from qualified experts in the area.

The "Journal of the Turkish German Gynecological Association" is a peer reviewed journal and adheres to the highest ethical and editorial standards. The Editorial Board of the journal endorses the editorial policy statements approved by the WAME Board of Directors. The journal is in compliance with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals published by the International Committee of Medical Journal Editors (updated August 2013, www.icmje.org). The editors also adhere to the Committee on Publications Ethics (COPE) recommendations (http://publicationethics.org).

Submission of manuscripts
All manuscripts must be submitted via the self explanatory online submission system which is available through the journal's web page at www.jtgga.org. Manuscripts submitted via any other medium will not be evaluated. During the submission please make sure to provide all requested information to prevent any possible delays in the evaluation process.

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

The figures should be submitted separately through the submission system in .JPG of .TIFF format. Please do not embed the figures in the main document. Make sure that the minimum resolution of each submitted figure is 300DPI.

A cover letter and a title page should be provided with all submissions. It should be stated in the cover letter that the manuscript was not previously published in any other publication, that it is not accepted for publication in another publication and that it is not under review for possible publication elsewhere.

Before completing your submission, please make sure to check the PDF proof of your manuscript which will be generated by the manuscript submission system and make sure that all items of the submission are displayed correctly.

Authors who have any queries regarding the submission process can contact the journal's editorial office:
Editorial Office:
Abdi İpekçi Caddesi 2/7 Nişantaşı, İstanbul / Turkey
+90 212 217 17 00
scholarone@jtgga.org

Editorial Policies
All manuscripts will be evaluated by the editorial board for their scientific contribution, originality and content. Authors are responsible for the accuracy of the data presented in their manuscript. The journal retains the right to make appropriate changes on the grammar and language of the manuscript when needed. When suitable the manuscript will be send to the corresponding author for revision. The manuscript, if accepted for publication, will become the property of the journal and copyright will be taken out in the name of the journal.

Full text of all articles can be downloaded at the web site of the journal www.jtgga.org

Preparation of Manuscripts
The "Journal of the Turkish German Gynecological Association" 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/),

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

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

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

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

Human and Animal Studies
Manuscripts submitted for publication must contain a statement to the effect that all human studies have been reviewed by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards described in an appropriate version of the 1975 Declaration of Helsinki, as revised in 2000. It should also be stated clearly in the text that all persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study should be omitted. Experimental animal studies should be presented with the disclosure of the appropriateness to the institutional/national/international ethical guides on care and use of laboratory animals.

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

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

In a cover letter the authors should state if any of the material in the manuscript is submitted or planned for publication elsewhere in any form including electronic media. The cover letter must contain address, telephone, fax and the e-mail address of the corresponding author.

Conflict of Interest
Authors must indicate whether or not they have a financial relationship with the organization that sponsored the research. They should also state that they have had full control of all primary data and that they agree to allow the Journal to review their data if requested. Therefore manuscripts should be accompanied by the "Conflict of Interest Disclosure Form." The form can be obtained from the journal webpage (www.jtgga.org).

Copyright
The author(s) transfer(s) the copyright to his/their article to the Journal of the Turkish German Gynecological Association effective if and when the article is accepted for publication. The copyright covers the exclusive and unlimited rights to reproduce and distribute the article in any form of reproduction (printing, electronic media or any other form); it also covers translation rights for all languages and countries. For U.S. authors the copyright is transferred to the extent transferable.

Submissions must be accompanied by the "Copyright Transfer Statement". The form is available for download on the journal's manuscript submission and evalu-

ation site. The copyright transfer form should be signed by all contributing authors and a scanned version of the wet signed document should be submitted.

Manuscript Specifications
Submissions should have the following parts.

Title Page
A separate title page should be submitted with all submissions and should include the title of the article, name(s), affiliations and major degree(s) of the author(s) and source(s) of the work or study, a short title (running head) of no more than 50 characters. The name, address, telephone (including the mobile phone number) and fax numbers and e-mail address of the corresponding author should be listed on the title page.

Abstract
All manuscripts should be accompanied by an abstract. A structured abstract is required with original articles and it should include the following subheadings: Objective, Material and Methods, Results and Conclusion. A structured abstract is not required with review articles and case reports. The abstract should be limited to 250 words for original articles and review articles and 150 words for case reports.

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

Original articles should have the following sections.

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

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

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

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. 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
State the importance and significance of your findings 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 those of others. Provide information on the limitations of the study. No new data are to be presented in this section.

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

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

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

Examples:
Journals;
Harrington K, Cooper D, Lees C, Hecher K, Campbell S. Doppler ultrasound of the uterine arteries: the importance of bilateral notching in the prediction of pre-eclampsia, placental abruption or delivery of a small-for-gestational-age baby. Ultrasound Obstet Gynecol 1996; 7: 182-8.

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

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

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

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.

Revisions
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 and 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.

Accepted articles
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.dtgg.de (Deutsch-Türkische Gynäkologengeselleschaft)
www.tajd.org (Türk-Alman Jinekoloji Derneği)
www.jtgga.org (Journal of the Turkish German Gynecological Association)

- Citation of published manuscripts in J Turk Ger Gynecol Assoc should be as follows: Tews G, Ebner T, Sommergruber M, Marianne M, Omar S. Ectopic Pregnancy in the Assisted Reproduction. J Turk Ger Gynecol Assoc 2004; 5: 59-62.

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

Journal of the
Turkish-German
Gynecological Association

Contents

Journal of the
Turkish-German
Gynecological Association

Editorial

Dear Colleagues,

I am delighted to present you to the third issue of the "Journal of the Turkish German Gynecological Association (JTGGA)" in the publishing year of 2014. Since the last few years, our objective was to collect more research studies and articles from Turkey and the international gynecology and obstetrics community. In this regard, we are glad that we are getting more qualitative submissions in comparison with the previous years with regards to be indexed by PubMed Central (PMC).

We worked hard to deliver you the journal with the best manuscripts in time. In this issue, you will read several good papers eagerly. There is a paper from Germany about the usage of misoprostol for preterm labor induction. It is obvious that today, epilepsy is the most common neurological disorder during pregnancy after migraine. Tonic-clonic seizures occurring during pregnancy appear to be associated with temporary hypoxia. An interesting paper that comes from Ankara deals with this issue. We have another paper that tries to determine if body mass index has an effect on the outcome of in vitro fertilization in patients with polycystic ovary syndrome undergoing controlled ovarian hyperstimulation. Vitamin D has important additional roles in many cellular events by virtue of its autocrine and paracrine effects. It leads to anti-inflammatory and anti-infective responses and regulates cellular proliferation, differentiation, and insulin synthesis. Recent studies have shown that vitamin D has an important role in both healthy pregnancy processes and long-term health of offspring. You will read a paper that shows the effect of place of residence and lifestyle on vitamin D deficiency in pregnancy. In this study, the eastern and western parts of Turkey are compared. Probably you all know that there is a limitation in the number of embryos to be transferred in our country. So we need a precision method to select the best embryo. We have a very good article on this subject where the outcomes of the embryos are compared with known implantation data based on dynamic scores to preconstructed embryo scoring model based on morphokinetic data. The importance of omental metastasis in patients with endometrial cancer has also been analyzed in another study.

We believe in the power of the meta-analyses. We have two meta-analyses in this issue with different subjects. One of them is about the technique of ovarian cystectomy in endometrioma surgery; while the other is ovarian aging and premature ovarian failure. In this issue, we also have two very interesting case reports and an informative quiz.

It is my pleasure to inform you that our foundation will restart the process of awarding scholarships to the successful colleagues studying in the field of Obstetrics and Gynecology with financial need and good academic standing. We will also support research projects which are in order to reach new findings in our field.

I would also like to acquaint you with the scientific activity of our sister association - DTGG. The symposium of the Deutsch-Türkische Gynäkologengesellschaft (German - Turkish Gynecology Association) will be held between 12:45 - 13:45 on October 8th, 2014 in Munich under the umbrella of the 60th Annual Congress of the German Association of Gynecology and Obstetrics.

Our journal is looking forward to obtain new reviewers who have adequate experience in the field of Obstetrics & Gynecology and are willing to take part in the evaluation process of the submitted manuscripts to our journal. Please do not hesitate to contact with us in order to apply to be a reviewer at JTGGA.

I wish to extend my heartfelt gratitude and appreciation to everyone who dedicated and sacrificed their time to deliver expertise, effort, and contribution to this publication and evaluation process, and I would welcome your participation and contributions in this journal as the loyal readers.

Best regards,

Cihat Ünlü, M.D.
Editor in Chief of JTGGA
President of TAJEV

Misoprostol for pre-term labor induction in the second trimester: Role of medical history and clinical parameters for prediction of time to delivery

Alexander di Liberto[1], Jan Endrikat[2], Sandra Frohn[2], Erich Solomayer[2], Kubilay Ertan[1,2]

[1]Department of Obstetrics and Gynecology, Leverkusen Municipal Hospital, Leverkusen, Germany

[2]Department of Obstetrics and Gynecology, Saarland University Hospital, Homburg, Germany

Abstract

Objective: Serious fetal malformations and/or chromosome aberrations detected by modern diagnostic tools in early pregnancy require discussions on induced abortion with pregnant women. Competent counseling includes prediction of the time needed for the whole abortion process. In an attempt to refine our predictions, we evaluated the impact of 11 medical history and clinical variables on time to delivery.

Material and Methods: We performed a retrospective chart analysis on 79 women submitted for pre-term abortion because of fetal anomalies. Abortion was induced by vaginal application of misoprostol (prostaglandine E_1, Cytotec™, Pfizer, New York, USA). We investigated 11 medical history and clinical variables for their impact on the percentage of women delivering within 24 hours (primary endpoint) and on the mean induction-delivery time interval (secondary endpoint).

Results: Fifty-three percent (42/79) of women delivered within 24 hours; 83.6% (66/79) delivered within 48 hours. A total of 83.3% of women with a history of late abortion delivered within 24 hours, whereas 50.7% without this history did. Mean induction-delivery time interval was 12.3 hours versus 35.5 hours, respectively. For history of early abortion, the figures were 65.2% versus 48.2% for delivery within 24 hours and 15.6 hours versus 32.5 hours for mean induction-delivery time interval. Current weight of fetus >500 g, weight of last previous newborn of ≤3500 g, previous pregnancies, premature rupture of membranes, and an elevated CRP of >0.5 mg/dL also cut time to delivery. Surprisingly, maternal and gestational age had no remarkable or consistent impact on the mean induction-delivery time interval. None of the differences reached statistical significance. Eighty-three percent of women needed 1000 μg or less for successful delivery.

Conclusion: Neither variables of medical history nor specific clinical variables allow for precise prediction of time to delivery in the second trimester. Certain parameters, however, show a trend to reduce the induction-delivery time interval. Our results might serve as initial guidance for patient counseling. (J Turk Ger Gynecol Assoc 2014; 15: 130-4)

Key words: Misoprostol, labor induction, time to delivery, patient counseling

Received: 06 March, 2014 **Accepted:** 17 June, 2014 **Available Online Date:** 08 August, 2014

Introduction

Today, modern prenatal diagnostic tools facilitate detection of the majority of fetal anomalies already in early pregnancy. In cases of serious fetal malformations and/or chromosome aberrations, the option of an induced abortion needs to be discussed with pregnant women.

In the second trimester, induced abortion is a two-step process, starting with application of a prostaglandin derivative followed by curettage. Currently, a number of prostaglandins (e.g., prostaglandin E_1 and E_2) and different application routes are available. Misoprostol (prostaglandine E_1, Cytotec™, Pfizer) has been licensed for the prevention and treatment of gastroduodenal ulcers since 1985 in more than 80 countries (1). Misoprostol has been extensively studied in gynecology and obstetrics and is widely recommended for the treatment of missed and incomplete miscarriages, the induction of abortion, cervical ripening before uterine instrumentation, and indication of labor in full-term pregnancies, although this is not an official indication by the label (off-label use) (1).

Prediction of the time from abortion induction to delivery, the so-called 'induction-delivery time interval,' is crucial for counseling pregnant women, as this phase constitutes a major emotional and psychological burden.

In an attempt to refine our predictions for the women, we evaluated the impact of 11 medical history and clinical variables on length of abortion.

Material and Methods

Study Design

We performed a retrospective analysis of 79 women treated at Leverkusen Municipal Hospital, Obstetrics and Gynecology

Address for Correspondence: *Alexander di Liberto, Department of Obstetrics and Gynecology, Leverkusen Municipal Hospital, Leverkusen, Germany. Phone: +49 214 133 34 28 e.mail: oppist@gmx.de*

DOI:10.5152/jtgga.2014.13034

Table 1. Baseline characteristics of study population (n=79)

Age (years)	≤18	18-30	31-34	>34	
n (%)	2/79 (2.5)	43/79 (54.4)	11/70 (13.9)	23/79 (29.1)	
Previous pregnancies	0	1	2	3	>3
	33/79 (41.8)	23/79 (29.1)	14/79 (17.7)	3/79 (3.8)	6/79 (7.6)
Previous deliveries	0	1	2	3	>3
	44/79 (55.7)	25/79 (31.6)	5/79 (6.3)	4/79 (5.1)	1/79 (1.3)
Gestational age (weeks)	≤13	≤16	≤21	≤25	≤29#
n (%)	1/79 (1.3)	9/79 (11.4)	35/79 (44.3)	30/79 (38.0)	2/79 (2.5)
Amniotic fluid	Normal	Oligohydramnios	Polyhydramnios	Anhydramnios	
n (%)	42/79 (53.2)	12/79 (15.2)	9/79 (11.4)	16/79 (20.3)	
Invasive diagnostics	No	CVS	AC	TORCH	Cordocentesis
n (%)	29 (36.7)	4/79 (5.1)	40/79 (53.2)	2/79 (2.2)	4/79 (4.3)

#>29 weeks: 2/79 (2.5%)
CVS: chorionic villus sampling; AC: amniocentesis; TORCH: toxoplasmosis/rubella/CMV/HSV

Table 2. Indications for induced abortion

Indication		**n (%)**
Chromosomal aberration	Total	18 (22.8)
	Trisomy 21	8 (44.4)
	Trisomy 18	2 (11.1)
	Trisomy 13	1 (5.6)
	Other trisomies	7 (38.9)
Organ malformation		17 (21.5)
Intrauterine fetal death		13 (16.5)
Multiple congenital malformations		9 (11.4)
Preterm premature rupture of membranes		5 (6.3)
Intrauterine growth retardation		5 (6.3)
CNS malformation		5 (6.3)
Fetal hydrops		5 (6.3)
Fetal infections		1 (1.3)
Twin to twin transfusion syndrome		1 (1.3)

(Teaching Hospital of the University of Cologne), by analyzing charts from April 2007-March 2009. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization - Good Clinical Practice (ICH-GCP) Guidelines of January 17, 1997. Ethical approval was not necessary because of the retrospective design of the study.

All women were submitted for pre-term abortion due to fetal malformations. Exclusion criteria were previous cesarean section and any other uterine surgery. We administered an initial dose of misoprostol (prostaglandin E_1, Cytotec™, Pfizer, New York, USA) of 200 μg vaginally on day 1. Within 24 hours - on day 2 - we continued by adding two further doses of 400 μg, at least 6 hours apart (maximum dose of 1000 μg/24 h). If no progress was seen, we repeated the doses of day 2 until delivery or conversion to another drug. Contraindications for misoprostol, such as allergies against misoprostol or any of the excipients, previous cesarean section, or other surgeries of the uterus, were respected.

Variables

We investigated the following medical history and clinical variables: age, previous pregnancies, gestational age, history of early abortion (up to 16 weeks of gestation), history of late abortion (more than 16 weeks), current fetus weight, weight of last previous newborn, years since last delivery, intrauterine fetal death, premature rupture of membranes (PROM), and C-reactive protein level (CRP).

The primary endpoint of this study was the percentage of women delivering within 24 hours (2,3); the secondary endpoint was the mean induction-delivery time interval.

Statistical Analysis

The data were analyzed by descriptive statistical methods. Differences between subgroups were analyzed using the Mann-Whitney U-test, the t-test, and odds ratios. The software BiAS. für Windows Version 9.2. (www.bias-online.de accessed 2014-02-09) was used.

Results

All 79 women were valid for our evaluation. Fifty-seven percent (45/79) of women were younger than 30 years; the median age was 30 (range 17-43). Forty-two percent (33/79) were never pregnant before, 55.7% (44/79) never delivered before, 97.5% (77/79) had ≤25 weeks of gestation, 46.8% (37/79) had an abnormal amount of amniotic fluid, and 63.3% (50/79) had invasive diagnostics prior to the induced abortion. The baseline characteristics of the study population are shown in Table 1.

The most frequent indications for pre-term labor induction were chromosome aberrations (22.8%, 18 women), organ malformations (21.5%, 17 women), and intrauterine fetal death (16.5%, 13 women) (Table 2).

Table 3. Deliveries within 24 hours and time to delivery by medical history

		Delivery ≤24 h		Time misoprostol - delivery	
		n	%	Mean (h)	Median (h)
Age (years) (n=79)	≤30	26/45	57.8	15.3	15.5
	>30	16/34	47.1	15.5	15.8
Previous pregnancies (n=79)	0	22/44	50.0	17.1	19.9
	>0	20/35	57.1	13.5	14.1
Gestational age (weeks) (n=79)	≤16	8/17	47.1	14.9	14.0
	>16	33/62	53.2	15.5	16.4
History of early abortion (n=79)	yes	15/23	65.2	15.6	15.5
	no	27/56	48.2	32.5	27.0
History of late abortion (n=79)	yes	5/6	83.3	12.3	13.5
	no	37/73	50.7	35.5	29.5
Current weight of fetus (n=79)	≤500 g	40/73	54.8	15.5	15.5
	>500 g	2/6	33.3	13.5	13.5
Weight of last previous newborn (n=35)	≤3500 g	16/26	61.5	12.1	11.8
	>3500 g	4/9	44.4	18.6	18.5
Years since last delivery* (n=35)	≤2	11/18	61.1	13.0	14.3
	>2	9/17	52.9	14.1	13.5
Intrauterine fetal death (n=79)	yes	9/17	52.9	17.6	20.4
	no	33/62	53.2	15.3	15.0
Premature rupture of membranes (n=79)	yes	7/11	63.6	13.7	13.5
	no	35/68	51.5	15.7	15.5
CRP (n=79)	≤0.5 mg/dL	33/63	52.4	15.9	11.8
	>0.5 mg/dL	9/16	56.3	13.6	12.0
Total		42/79	53.2	16.65	15.4

*incl. late abortions

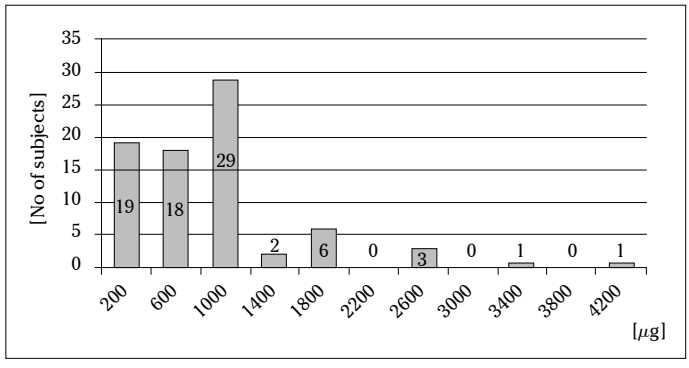

Figure 1. Number of women by total misoprostol dose

A total of 53.2% (42/79) of women delivered within 24 hours, and 83.6% (66/79) delivered within 48 hours. The most important factor impacting the induction-delivery time interval was history of late or early abortion: 83% of women with a history of late abortion delivered within 24 hours whereas 50.7% without this history did. Also, the mean induction-delivery time interval was 12.3 hours versus 35.5 hours (p=0.09). A similar feature was seen in women with a history of early abortion; 65.2% vs. 48.2% delivered within 24 hours, and the mean induction-delivery time interval was approximately half as long for these women, i.e., 15.6 versus 32.5 hours (p=0.075).

Fifty-five percent of women with current fetus weight ≤500 g delivered within 24 hours, whereas 33.3% did with a larger fetus. Time to delivery was also 2 hours less. Interestingly, a weight of last previous newborn of ≤3500 g facilitated timely delivery. A total of 61.5% of women delivered within 24 hours, approximately 6 hours faster than women with larger previous newborns (delivery within 12 hours vs. 18 hours). Slightly more women with previous pregnancies delivered within 24 hours (57.1 vs. 50.0% for nulligravidae); however, the mean induction-delivery time interval was 4 hours shorter (13.5 vs. 17.1 hours). Premature rupture of membranes and an elevated CRP of >0.5 mg/dL reduced the mean induction-delivery time interval by approximately 2 hours. Also, intrauterine fetal death slightly prolonged mean time to delivery (2 hrs). Surprisingly, the women's age and gestational age had no remarkable or consistent impact on the mean induction-delivery time interval (Table 3). None of the evaluations of the medical history and clinical variables reached statistical significance.

Figure 1 shows the number of women and their total misoprostol dose. The majority, 83.5% (66/79), needed 1000 μg or less for

Table 4. Total mean misoprostol dose by medical history

		Misoprostol dose (μg)
Age (years) (n=79)	≤30	840
	>30	965
Previous pregnancies (n=79)	0	936
	>0	886
Gestational age (weeks) (n=79)	≤16	1235
	>16	819
Current weight of fetus (n=79)	≤500 g	912
	>500 g	933
Premature rupture of membranes (n=79)	yes	818
	no	929

successful delivery. That was one dose of 200 μg on day 1 and 2x200 μg on days 2 and 3.

Table 4 shows the total mean misoprostol dose by medical history. Only for women with a gestational age of ≤16 weeks did the mean misoprostol dose exceed 1000 μg (i.e., 1235 μg).

Six women (7.6%) suffered prolonged bleeding post-surgery, reaching anemia of <9.5g/dL hemoglobin, but no blood transfusions were necessary. Two women experienced fever (data not shown).

Discussion

In an attempt to define the role of medical history and/or clinical variables for the prediction of time to delivery in the second trimester, we performed a retrospective chart analysis on 79 women. All were submitted for pre-term labor induction due to fetal and amniotic fluid anomalies, i.e, chromosome aberrations, PROM, or a wide spectrum of malformations.

We defined the percentage of women delivering within 24 hours as the primary endpoint, a well-established measure for successful abortion induction (2, 3). After repeated vaginal application of misoprostol, overall, 53% of women delivered within 24 hours. This result is well in line with other studies, irrespective of the misoprostol dose: Kolderup reported a success rate of 77% (4), whereas Manjunath (5) even reached 82.4%. However, all of these studies were relatively small, and the group of women might not be directly comparable with respect to all of the relevant medical history and/or clinical baseline characteristics. Our secondary endpoint, the mean time to delivery, is of more practical use for patient counseling, as it provides the treating physician a rough estimate of the induction-delivery time interval for a specific subject with a unique medical history and clinical profile. Here, we feel our data are unique.

Our analysis of the impact of previous late or early abortions on successful delivery within 24 hours is somewhat innovative, as we were not able to find comparable studies in the current literature. Our data show that a total of 83.3% (5/6) of women with a history of late abortion delivered within 24 hours, whereas 50.7% (37/73) without this history did. This finding is supported by the mean induction-delivery time interval, which was 12.3 hours and 35.5 hours, respectively (p=0.09). Although this result does not reach statistical significance - most probably due to the small sample size - we tend to suggest at least a positive trend for late abortions in the medical history to abbreviate the induction-delivery time interval for later abortions. We would propose further research to investigate whether or not persistent cervical infections, which frequently cause late abortions, might impact cervical ripening during induction of abortion.

We found a similar effect for history of early abortion: 65.2% (15/23) delivered within 24 hours compared to 48.2% (27/56) without this history. The mean induction-delivery time interval confirmed this trend, with results of 15.6 hours versus 32.5 hours (p=0.075). Here, the sample sizes were more balanced but still not sufficient to confirm statistical significance.

Weight of fetus ≤500 g increased the likelihood of successful delivery within 24 hours. As the vast majority of our cohort consisted of women seeking pre-term abortion in the second trimester, 92.4% (73/79) of women bore a fetus of ≤500 g. The median fetus weight was 240 g. Interestingly, we did not find any similar reports on pre-term labor induction in the recent literature just for labor induction in the third trimester. Crane et al. (3) reported a direct correlation between lower birth weight and delivery within 24 hours and also a lower rate of cesarean sections, quite obvious findings. However, these results are barely comparable with ours.

A limitation of our findings is the somewhat poor accuracy of the pre-natal weight assessment. In our study, we used the precise results of postpartum weights, but for patient counseling, one must rely on pre-natal assessments by ultrasound, which feature a variation of about 15% on average, depending on the quality of the method of measurement, the ultrasound technique, and the experience of the operator (5).

Premature rupture of membranes and an elevated CRP of >0.5 mg/dL also shorten time to delivery by approximately 2 hours. Again, we were unable to find a comparable trial in the recent literature. Only Mbele et al. (6) showed a significantly reduced time to delivery after premature rupture of membranes but in a cohort of women with full-term pregnancies.

Surprisingly, the women's age and gestational age had no remarkable or consistent impact on the mean induction-delivery time interval. Although slightly more women with gestational age ≤16 weeks delivered within 24 hours (53.2% vs. 47.1% for women ≤16 weeks), the mean time to delivery was almost 15 hours for both groups. Edwards et al. (7), Murchison et al. (8), and Lister et al. (9) investigated different regimens of misoprostol for first-trimester abortions in similar cohorts as ours. The success rates varied from 54% and 81% (8) to 78% (9) and 83% (10). Unfortunately, no separate evaluations by gestational age were reported. Only data on misoprostol and gestational age are available for the third trimester. Wing et al. (2) studied a cohort of 1373 women and found a significant positive correlation between gestational age and successful delivery within 24 hours-i.e., the higher the gestational age, the shorter the delivery time. In addition, the more advanced the pregnancy, the smaller the misoprostol dose that was needed.

The major limitations of our study are not only the small sample size and the multitude of anamnestic and clinical variables but

also the wide range of gestational ages (including the different density of myometrial receptors for contractile agents) and the diversity of indications leading to the induced abortion. In order to get scientifically robust and statistically convincing results, a cohort is needed that allows for clustering of variables, i.e, looking at women that differ just for one variable. Such a study design, however, is only possible in a large multicenter approach.

In this study, we tried to define the role of medical history and/or clinical variables for prediction of time to delivery for a cohort of women in the second trimester. Although our results did not reach statistical significance, most reasonably due to the small sample size, we saw at least trends for certain variables. We provide approximations for the mean induction-delivery time interval, which might serve as some preliminary guidance for the physician. Only few studies in a similar cohort have been reported so far. More knowledge is available for the third trimester, which is, however, not really comparable. In addition, the few studies with a similar study design did not analyze the findings in such a detailed manner as we did. Eventually, due to the paucity of findings on the subject reported here, even our non-significant results could be considered a valuable contribution to broaden our understanding of the duration of pre-term abortion induction.

In conclusion, neither variables of medical history nor specific clinical variables allow for precise prediction of time to delivery in the second trimester. Certain parameters, such as history of late/early abortions, current weight of fetus >500 g, weight of last previous newborn ≤3500 g, previous pregnancies, premature rupture of membranes, and elevated CRP of >0.5 mg/dL, however, show a trend to reduce the induction-delivery time interval. Our results might serve as initial guidance for patient counseling, which is crucial for compliance. Eventually, well-founded information about the abortion course could improve the psychological situation.

Ethics Committee Approval: *N/A.*

Informed Consent: *N/A.*

Peer-review: *Externally peer-reviewed.*

Author contributions: *Concept - A.dL., K.E., S.F.; Design - A.dL., K.E., S.F.; Supervision - A.dL., K.E., S.F., E.S.; Resource - A.dL., S.F.; Materials - A.dL., S.F.; Data Collection&/or Processing - A.dL., J.E., S.F.; Analysis&/or Interpretation - A.dL., K.E., S.F., J.E., E.S.; Literature Search - S.F., J.E.; Writing - J.E., S.F.; Critical Reviews - A.dL., K.E., S.F., J.E.,E.S.*

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

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

References

1. Weeks AD, Fiala C, Safar P. Misoprostol and the debate over off-label drug use. BJOG 2005; 112: 269-72. [CrossRef]
2. Wing DA, Tran S, MD, Paul RH. Factors affecting the likelihood of successful induction after intravaginal misoprostol application for cervical ripening and labor induction. Am J Obstet Gynecol 186; 2002: 1237-43. [CrossRef]
3. Crane JM, Delaney T, Butt KD, Bennett KA, Hutchens D, Young DC. Predictors of successful labor induction with oral or vaginal misoprostol. J Matern Fetal Neonatal Med 2004; 15: 319-23. [CrossRef]
4. Kolderup L, McLean L, Grullon K, Safford K, Kilpatrick SJ. Misoprostol is more efficacious for labor induction than prostaglandine E2, but is it associated with more risk? Am J Obstet Gynecol 1999; 180: 1543-50. [CrossRef]
5. Dudley NJ. A systematic review of ultrasound estimation of fetal weight. Ultrasound Obstet Gynecol 2005; 25: 80-9. [CrossRef]
6. Mbele AM, Makin JD, Pattison. Can the outcome of induction of labour with oral misoprostol be predicted? S Afr Med J 2007; 97: 289-92.
7. Edwards RK, Sims SM. Outcomes of second-trimester pregnancy terminations with misoprostol: Comparing two regimens. Am J Obstet Gynecol 2005; 193: 544-50. [CrossRef]
8. Murchison A, Duff P. Misoprostol for uterine evacuation in patients with early pregnancy failures. Am J Obstet Gynecol 2004; 190: 1445-6. [CrossRef]
9. Lister MS, Shaffer LE, Bell JG, Lutter KQ, Moorma KH. Randomized, double-blind, placebo-controlled trial of vaginal misoprostol for management of early pregnancy failures. Am J Obstet Gynecol 2005; 193: 1338-43. [CrossRef]

The effects of a history of seizures during pregnancy on umbilical arterial blood gas values in pregnant women with epilepsy

Özhan Özdemir, Mustafa Erkan Sarı, Funda Arpacı Ertuğrul, Aslıhan Kurt, Vefa Selimova, Cemal Reşat Atalay
Department of Obstetrics and Gynecology, Ankara Numune Training and Education Hospital, Ankara, Turkey

Abstract

Objective: The objective of this study is to investigate if the number of seizures that occur during pregnancy has any effect on umbilical arterial blood gas values at delivery.

Material and Methods: In total, 55 women who were 37 to 41 weeks pregnant and diagnosed with generalized tonic-clonic epilepsy and 50 pregnant women with similar characteristics but not diagnosed as epileptic were included in this study. The patients diagnosed with epilepsy were divided into two groups: 27 patients with a history of at least 5 epileptic seizures during pregnancy and 28 who had no seizures during pregnancy. All patients diagnosed with epilepsy had a history of caesarean delivery or a caesarean section under general anesthesia on the advice of neurology. Pregnant women in the control group were also chosen from among patients who had a caesarean on account of a previous caesarean delivery. In the cases included in the study, umbilical arterial blood gas sampling was performed immediately after delivery.

Results: When the control group without epilepsy was compared with pregnant women who had no history of epileptic seizures during pregnancy, no difference was found in umbilical arterial blood gas values ($p>0.05$). When patients with a history of 5 or more epileptic seizures during pregnancy were compared with the control group without epilepsy and the patients with epilepsy who had no history of seizures during pregnancy, there was no statistically significant difference ($p>0.05$), although their umbilical arterial blood pH values were found to be lower, while partial carbon dioxide pressure (pCO_2), values were higher and partial oxygen pressure (pO_2) values were lower.

Conclusion: Taking potential fetal risks into consideration, maternal generalized tonic-clonic epileptic seizures might be worrying. Tonic-clonic seizures that occur during pregnancy appear to be associated with temporary hypoxia. Therefore, monotherapy for seizures and treatment at the lowest effective dose should be administered to women with epilepsy in the preconception and prenatal term.

(J Turk Ger Gynecol Assoc 2014; 15: 135-9)

Key words: Epilepsy, pregnancy, umbilical arterial blood gas

Received: 11 June, 2014 **Accepted:** 21 July, 2014

Introduction

Advances in the diagnosis of and treatment for epilepsy have allowed many women with epilepsy to lead a normal life and to conceive. Today, epilepsy is the most common neurological disorder during pregnancy, after migraine. Comprehensive epidemiological studies reveal that the prevalence of epilepsy is 6.8%, and 0.3% to 0.5% of pregnancies are accompanied by epilepsy (1). Pregnant women with epilepsy are worried that antiepileptic drugs may have negative effects on the fetus, that convulsion frequency may increase, and that some health problems, including epilepsy, may occur in their children. Furthermore, it is known that antiepileptic drugs increase the risk of congenital malformation (2).

In women with epilepsy, such pregnancy complications as hyperemesis gravidarum, vaginal bleeding, preeclampsia, preterm birth, and postpartum bleeding are more common (3). Besides studies suggesting that seizures occurring in the first trimester increase malformation risk, there are also those that reject this idea (4). It has been indicated that central nervous system disorders, such as microcephaly, chronic static encephalopathy, and cerebral palsy, are more common in children affected by in utero seizures (5).

Generalized tonic-clonic seizures are harmful to the fetus due to an increase in blood pressure, oxygenation, and electrolyte changes during a seizure. Seizure-related traumas, spontaneous miscarriages, and intrauterine deaths may also occur (6). It has been shown in cardiotocography follow-ups that during term pregnancy, generalized tonic-clonic seizures lead to temporary fetal asphyxia. Fetal bradycardia, a decrease in variability, and decelerations may be observed for 15 minutes following a seizure (6).

Intrapartum assessment of umbilical cord arterial blood gas values is a decisive method of diagnosis in birth management. In addition, by giving a retrospective idea about fetal well-being at delivery, it contributes to the management of neonatal term and to decisions about possible attempts at

Address for Correspondence: *Özhan Özdemir, Department of Obstetrics and Gynecology, Ankara Numune Training and Education Hospital, Ankara, Turkey. Phone: +90 505 225 50 78 e.mail: seyozi@hotmail.com*

DOI:10.5152/jtgga.2014.13118

Table 1. The distribution of age, gestation period (weeks), birth weight, and 5-minute Apgar scores

Group	Age	Gestation Period	Birth Weight	5th minute Apgar Scores
Pregnant women with epilepsy who had no seizures (n=28)	26.4±6.1	38.7±0.9	3192.17±377.6	8.2±0.3
Pregnant women with epilepsy who had at least 5 seizures (n=27)	26.5±5.8	38.2±1.1	3031.67±384.3	8.0±0.7
Pregnant women without epilepsy (n=50)	27.1±5.8	38.6±1.2	3211.43±364.2	8.3±0.5

neonatal resuscitation in this term (7). Appearance, Pulse, Grimace, Activity, Respiration (APGAR) scoring might be beneficial in distinguishing normal neonates and the ones evidently exposed to hypoxia. However, this method of scoring is not sensitive enough to distinguish babies affected to a lesser extent by hypoxia (8). Thus, being an indicator of intrapartum condition during delivery and neonatal prognosis after delivery, umbilical cord pH values have been paid close attention in recent years.
Our aim in this study is to explain whether epileptic seizures that occur during pregnancy are associated with antepartum asphyxia. For this purpose, we made use of umbilical arterial blood gas measurement as one of the most objective indicators of asphyxia.

Material and Methods

The study was conducted in Ankara Numune Education and Research Hospital. The protocol of the study was approved by the ethics committee of the hospital, and all participants signed an informed consent. In total, 55 women who were 37 to 41 weeks pregnant and diagnosed with generalized tonic-clonic epilepsy and 50 other pregnant women with similar characteristics but not diagnosed as epileptic were included in the study. All pregnant women with epilepsy were patients who had been diagnosed as epileptic by a neurology clinic before pregnancy. The mean age, mean gestation period (weeks), and mean birth weight of the patients included in the study were recorded.
The patients diagnosed with epilepsy were divided into two groups: 27 patients with a history of at least 5 epileptic seizures during pregnancy and 28 who did not have any seizures during pregnancy. All patients diagnosed with epilepsy had a history of caesarean delivery or a caesarean section under general anesthesia on the advice of neurology, and those who had a vaginal delivery were not included in the study in order to eliminate differences likely to arise from the mode of delivery. Pregnant women in the control group were also chosen from among patients who had an elective caesarean section because of a previous caesarean delivery.
In these cases, umbilical cord arterial blood gas sampling was performed immediately after delivery. Blood gases were analyzed within 30 minutes of birth by double-clamping a minimum 10-centimeter segment of cord within 5 minutes of birth and taking blood samples from the artery. To prevent blood from congealing in the syringes, heparinized blood gas syringes were used. The analyzer (ABL-2 Analyzer; Radiometer, Copenhagen, Denmark) was used to define blood gas parameters. Arterial pH, partial carbon dioxide pressure (pCO_2), partial oxygen pressure (pO_2), bicarbonate levels (HCO_3), and base excess (BE) were measured separately by the analyzer.
Those who had maternal diseases, such as diabetes mellitus and hypertension, which are likely to cause uteroplacental insufficiency, and pregnancies complicated by intrauterine growth retardation and oligohydramnios were not included in the study. Patients with highly variable decelerations that had signs of fetal distress in fetal heart rate (less than 70 beats per minute over 60 seconds), those observed to have recurrent late decelerations, and those who had an epileptic seizure at delivery were not included in the study, either. The 1- and 5-minute APGAR scores after birth were recorded. Umbilical arterial blood gas samples of the patient groups who had epileptic seizures during pregnancy and who did not were compared with each other and with the control group.
Statistical data was acquired using the Statistical Package for the Social Sciences for Windows version 17.0 (SPSS, Chicago, IL, USA) for Windows program. The mean±standard deviation was used as descriptive statistics. Whether continuous variables were normally distributed or not was analyzed using Kolmogorov-Smirnov test. Significance between the groups was assessed by means of independent samples t-test and Anova test. In the assessments, the predicted error rate was $\alpha=0.05$.

Results

The mean age, mean gestation period (weeks), and mean birth weight of the patients with and without epilepsy included in the study are shown in Table 1. When the three groups were compared with each other, no statistical difference was found regarding the, gestation period, and birth weight ($p>0.05$). In all instances, the 1- and 5-minute APGAR scores were found to be ≥7.
While 5 (17%) of the patients who had no history of seizures during pregnancy were not taking antiepileptic drugs, 2 (8%) were receiving polytherapy and 21 (75%) were receiving monotherapy. Two (7%) of the patients with a history of 5 or more seizures during pregnancy were receiving polytherapy, and 25 (93%) were receiving monotherapy (Table 2).
The distribution of umbilical arterial blood gas values of the patients included in the study is shown in Table 3. When 55 pregnant women with epilepsy included in the study were compared with 50 pregnant women constituting the control group, although their umbilical arterial blood pH values were found to be lower, pCO_2 values were higher, and pO_2 values were lower, no statistically significant difference was found between the groups ($p>0.05$).

When the control group without epilepsy was compared with the pregnant women without a history of epileptic seizures during pregnancy, no difference was found in umbilical arterial blood gas values (p>0.05).
When the patients with a history of 5 or more epileptic seizures during pregnancy were compared with the control group without epilepsy and patients with epilepsy who had no history of seizures during pregnancy, although their umbilical arterial blood pH values were found to be lower, pCO_2 values were higher, and pO_2 values were lower, there was no statistically significant difference (p>0.05).
Moreover, when other blood gas parameters were assessed, no difference was found between the three groups regarding base excess and HCO_3 levels (p>0.05).

Discussion

Intrapartum assessment of umbilical cord arterial blood gas values is a decisive method of diagnosis in birth management.

Table 2. Distribution of antiepileptic therapy in patients

	Pregnant women with epilepsy who had no seizures (n=28)	Pregnant women with epilepsy who had at least 5 seizures (n=27)
No use of antiepileptic drugs, n	5	-
Carbamazepine monotherapy, n	9	11
Lamotrigine monotherapy, n	4	5
Valproic acid monotherapy, n	4	4
Oxcarbazepine monotherapy, n	2	3
Levetiracetam monotherapy, n	2	2
Carbamazepine and levetiracetam polytherapy, n	2	1
Valproic acid and lamotrigine polytherapy, n	-	1

In addition, as a retrospective idea about fetal well-being during delivery, it contributes to the management of the neonatal term and to decisions about possible attempts at neonatal resuscitation in this term. Umbilical cord blood gas measurement performed at delivery is an objective indicator of fetal acid-base balance, and it is also accepted as the fetal response to birth (9). When the umbilical cord arterial blood pH value is ≤7.20, the condition is defined as fetal acidosis; however, a pH of ≤7.0 is considered pathological acidosis. In term neonates born with an umbilical cord arterial blood pH of >7.0, no increase has been observed in long-term morbidity (10).
As for APGAR scoring, it might be beneficial in distinguishing normal neonates and the ones severely affected by hypoxia. This method of scoring, however, is not sensitive enough to distinguish babies affected to a lesser extent by hypoxia (8). Therefore, as an indicator of intrapartum condition during delivery and neonatal prognosis after delivery, umbilical cord pH values have been focused on in recent years (11). Umbilical fetal blood gas pH and other measures are reported to be more valuable in terms of yielding fewer false-positive results in the differential diagnosis. Thus, after delivery, in distinguishing babies exposed to hypoxia, the determination of umbilical cord blood gases is adopted, along with the use of intrapartum electronic fetal monitoring (12).
The answer to the question "Which artery should umbilical cord blood gases be drawn from?" should naturally be the umbilical artery, as it better reveals fetal well-being. The reason for this is that in the case of fetal acidemia and hypoxia, changes first occur in umbilical arterial blood gases. Moreover, when umbilical cord venous blood gas values are at normal levels, acidemia may occur in the umbilical artery (11). Therefore, in this study, umbilical arterial blood gas parameters were analyzed.
When carbon dioxide that has formed on fetal tissues is not eliminated through uteroplacental circulation, pCO_2 increases and respiratory acidosis occurs. If fetal tissues are insufficiently oxygenated, the activation of the anaerobic pathways for glucose utilization results in lactic acid accumulation and metabolic acidosis. At delivery, changes occur in factors affecting gas flow in uteroplacental circulation and, according to their significance, in umbilical cord blood gas parameters.
The effects of epileptic seizures during pregnancy on the fetus have always been worrying. Maternal epileptic seizures may cause fetal hypoxia, leading to changes in umbilical arterial blood gas. Generalized tonic-clonic seizures are harmful to the fetus due to the resulting increase in blood pressure, oxygenation, and electrolyte changes during a seizure. In addition,

Table 3. The results of the umbilical arterial blood gas analysis

Group	pH	pCO_2 (mmHg)	pO_2 (mmHg)	HCO_3 (mmol/L)	Base Excess (mmol/L)
Pregnant women with epilepsy who had no seizures (n=28)	7.24±0.08	53.1±11.5	16.1±5.7	23.3.±5.1	-4.3±2.2
Pregnant women with epilepsy who had at least 5 seizures (n=27)	7.22±0.03	55.1±10.2	14.4±4.26	22.1±5.0	-4.7±1.9
Control group without epilepsy (n=50)	7.24±0.05	52.1±11.2	17.7±5.21	23.1±5.0	-4.1±2.1
pCO_2: partial carbon dioxide pressure; pO2: partial oxygen pressure; HCO3: bicarbonate levels					

the increase in intrauterine pressure during a seizure may also decrease uteroplacental blood flow (6). It has been shown in cardiotocography follow-ups that in term pregnancy, generalized tonic-clonic seizures cause temporary fetal asphyxia. Fetal bradycardia, a decrease in variability, and decelerations may be observed for 15 minutes following a seizure (6). Fetal damage may be caused by metabolic changes attributable to prolonged generalized tonic-clonic seizures (13). Prolonged generalized tonic-clonic seizures may even result in fetal bradycardia and fetal death, even in the absence of maternal hypoxia (14).

Umbilical arterial blood gas values may not only be affected by such pathological conditions as uteroplacental insufficiency, causing intrauterine growth retardation, but also change depending on gestation period, the mode of delivery, and the type of anesthesia administered. In the relevant literature, it has been pointed out that there is no significant correlation between birth weight and blood gases; however, in cases of intrauterine growth retardation associated with uteroplacental insufficiency, fetal metabolic acidemia may occur (15). In our study, there was no difference between the groups with and without a history of seizures during pregnancy with respect to birth weight, and all cases were in term pregnancy. Studies indicate that umbilical arterial blood gas values in vaginal deliveries were found to be lower compared to those in caesarean section deliveries (16). Therefore, to be able to determine the effects of patients with epilepsy on blood gas, only pregnant women with epilepsy who had a caesarean delivery were included in our study, and the control group consisted of the patients who had an elective caesarean section.

The type of anesthesia administered during caesarean delivery, whether general or regional, does not have an effect on umbilical arterial blood gases (17). However, when the mother is under general or regional anesthesia, increased length of time from uterine incision to delivery (especially an interval of longer than 3-5 minutes) and prolonged exposure to inhalation agents under general anesthesia lead to low APGAR scores and acidosis in neonates (18). In another study, it has been stated that in babies born after a long induction-to-uterotomy and uterotomy-to-delivery time interval, umbilical arterial pH values and APGAR scores were found to be low (19). In our study, all of our patients delivered their babies under general anesthesia, and in all cases, the time interval from skin incision to the delivery of the baby was recorded to be shorter than 3 minutes. Moreover, not using inhalation agents until the umbilical cord was clamped allowed us to avoid negative effects on blood gas. In term caesarean deliveries, "normal" umbilical arterial blood gas values were indicated as follows: pH 7.27 (7.15-7.38), pCO_2 49 (32-68) mm Hg, HCO_3 22.3 (15.4-26.8) mEq/L, and base excess -4 (-8.1-0.9) mEq/L (20). Umbilical arterial pO_2 values were not found to be associated with any adverse neonatal outcomes (21).

There is a complex relationship between fetal asphyxia (antepartum and intrapartum), neonatal asphyxia, and possible resulting brain damage. The severity, duration, and nature of asphyxia are affected by the cardiovascular compensatory response. Asphyxia is defined as a condition of impaired blood gas exchange, which may lead to progressive hypoxemia and hypercapnia (22). According to the American College of Obstetricians and Gynecologists, it is also a clinical situation of damaging hypoxia and metabolic acidosis (21). Asphyxia may also occur temporarily without causing pathologic sequelae. However, when a fetus is severely affected by asphyxia, it may result in a decrease in oxygenation of tissues, acid accumulation, and metabolic acidosis. A blood gas and acid-base assessment should be carried out for the diagnosis of intrapartum fetal asphyxia. The crucial question for clinicians is "What is the threshold of metabolic acidosis above which fetal morbidity and mortality may occur?"

Low and colleagues have suggested a scoring system aimed at predicting neonatal encephalopathy and defined umbilical arterial base deficits at birth as mild at 4-8 mmol/l, moderate at 8-12 mmol/l, and severe at greater than 12 (23). It has been shown that the incidence of minor motor and cognitive defects among term neonates exposed to mild antepartum fetal asphyxia increased at the age of 4-8, compared to those not exposed to asphyxia (24). Some criteria have been laid down to define an acute intrapartum hypoxic event as sufficient to be a cause of cerebral palsy. In an umbilical cord arterial blood analysis performed at delivery, pH <7 and base deficit ≥12 have been reported as evidence of metabolic acidosis (21).

In our study, we aimed to clarify whether epileptic seizures that occur during pregnancy are associated with antepartum asphyxia. For this purpose, we made use of the umbilical cord arterial blood gas measurement, which remains one of the most reliable indicators of asphyxia. In our study, when the control group without epilepsy and the pregnant women without a history of epileptic seizures during pregnancy were compared, no difference was found regarding umbilical arterial blood gas values, and it was demonstrated that controlled pregnancies that were complicated by epilepsy were not associated with chronic hypoxia or antepartum asphyxia.

Although the negative effects of prolonged epileptic seizures on the fetus have been revealed, it is obvious that exposure to fetal hypoxia will also increase as the number of seizures increases during pregnancy. In our study, when the pregnant women with a history of 5 or more epileptic seizures during pregnancy were compared with those with epilepsy who had no history of seizures during pregnancy, although there was no statistically significant difference between them, their umbilical arterial blood pH values were found to be lower, pCO_2 values were higher, and pO_2 values were lower.

In the relevant literature, it has been demonstrated that the rate of pregnancy complications and adverse perinatal outcomes increases in pregnancies in women with epilepsy. Most of such pregnancies, however, go to full term without problems (25). It has been reported that during pregnancy, 48%-57% of pregnant women with epilepsy have no change in seizure frequency, 25%-33% experience an increase, and 9%-22% have a decrease in seizure frequency (26). The most important factor that is believed to cause an increase in seizure frequency is to stop taking antiepileptic drugs during pregnancy. Expectant mothers stop taking antiepileptic drugs, especially in the course of the first 3 months of their pregnancy, to avoid potential negative effects of these drugs on their babies. Childbirth is a process in

which epileptic attacks are triggered. At delivery, the risk of having an attack increases to 9 times as likely. Therefore, great care should be taken at delivery, and the patient should deliver by caesarean section when required. If recurrent seizures occur at delivery, caesarean section should be performed under general anesthesia because of the risk of fetal anoxia.

In conclusion, pregnancies in women with epilepsy pose unique challenges to expectant mothers. The follow-up of pregnant women with epilepsy requires good teamwork between an obstetrician and a neurologist suitably experienced in management issues for such cases. By adopting a balanced approach and monitoring appropriate follow-up of these patients, it is possible to achieve favorable pregnancy outcomes in women with epilepsy-basically the same as those in the general population. As there are potential fetal risks, maternal generalized tonic-clonic epileptic seizures might be alarming. Thus, with the administration of optimal treatment, epileptic seizure control should be provided during pregnancy so as to reduce the risk of convulsions to a minimum. It is recommended that monotherapy for seizures and treatment at the lowest effective dose should be administered to pregnant women with epilepsy in the preconception and prenatal terms.

Ethics Committee Approval: *Ethics committee approval was received for this study from the local ethics committee.*

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

Peer-review: *Externally peer-reviewed.*

Author contributions: *Concept - Ö.Ö.; Design - Ö.Ö.; Supervision - M.E.S.; Resource - F.A.E.; Materials - V.S., A.K.; Data Collection&/or Processing - V.S., A.K.; Analysis&/or Interpretation - Ö.Ö., M.E.S.; Literature Search - Ö.Ö., M.E.S.; Writing - Ö.Ö.; Critical Reviews - C.A.*

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

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

References

1. Richmond JR, Krishnamoorthy P, Andermann E, Benjamin A. Epilepsy and pregnancy: An obstetric perspective. Am J Obstet Gynecol 2004; 190: 371-9. [CrossRef]
2. Dravet C, Julian C, Legras C, Magaudda A, Guerrini R, Genton P, et al. Epilepsy, antiepileptic drugs, and malformations in children of women with epilepsy: A French prospective cohort study. Neurology 1992; 42 (4 Suppl 5): 75-82.
3. Yerby M, Koepsell T, Daling, J. Pregnancy complications and outcomes in a cohort of women with epilepsy. Epilepsia 1985; 26: 631-5. [CrossRef]
4. Lindhout D, Meinardi H, Meijer JW, Nau H. Antiepileptic drugs and teratogenesis in two consecutive cohorts: changes in prescription policy paralleled by changes in pattern of malformations. Neurology 1992; 42 (4 Suppl 5): 94-110.
5. Nelson KB, Ellenberg JH. Maternal seizure disorder, outcome of pregnancy, and neurologic abnormalities in the children. Neurology 1982; 32: 1247-54. [CrossRef]
6. Teramo K, Hiilesmaa V, Bardy A, Saarikoski S. Fetal heart rate during a maternal grand mal epileptic seizure. J Perinat Med 1979; 7: 3-6. [CrossRef]
7. ACOG Committee on Obstetric Practice. ACOG Committee Opinion No. 348, November 2006: Umbilical cord blood gas and acid-base analysis. Obstet Gynecol 2006; 108: 1319-22. [CrossRef]
8. Yeomans ER, Hauth JC, Gilstrap LC, Strickland DM. Umbilical cord pH, PCO2 and bicarbonate following uncomplicated term vaginal deliveries. Am J Obstet Gynecol 1985; 151: 798-800. [CrossRef]
9. Goldaber KG, Gilstrap LC. Correlations between clinical events and umbilical cord blood acid-base and blood gas values. Clin Obstet Gynecol 1993; 36: 47-59. [CrossRef]
10. Gordon A, Johnson JW. Value of umbilical blood acid-base studies in fetal assessment. J Reprod Med 1985; 30: 329-36.
11. Benian A, Uludağ S, Atış A, Gök M, Madazlı R. Analysis of umbilical cord blood acid-base status at birth. Cerrahpasa J Med 2002; 33: 236-44.
12. Gilstrap LC. Fetal Acid-base Balance. In: Creasy RK, Resnik R, editors. Maternal-Fetal Medicine. Philadelphia: WB Saunders; 1998. p. 331.
13. Minkoff H, Schaffer R, Delke I, Grunebaum N. Diagnosis of intracranial hemorrhage in utero after a maternal seizure. Obstet Gynecol 1985; 65 (3 Suppl): S22-24.
14. Hiilesmaa VK, Teramo K, Bardy AH. Social Class, Complications, and Perinatal Deaths in Pregnancies of Epileptic Women: Preliminary Results of the Prospective Helsinki Study. In: Janz D, editors. Epilepsy, Pregnancy, and the Child. New York: Raven Press; 1982. p. 87-90.
15. Atalla RK,Abram SK, Bell SC, Taylor DJ. Newborn acid-base status and umbilical cord morphology. Obstet Gynecol 1998; 92: 865-8. [CrossRef]
16. Thorp JA, Dildy GA, Yeomans ER, Meyer BA, Parisi VM. Umbilical cord blood gas analysis at delivery. Am J Obstet Gynecol 1996; 175: 517-22. [CrossRef]
17. Li CH, Zhu CX, He J. Effects of general anesthesia for cesarean section on infants. Zhonghua Fu Chan Ke Za Zhi 2006; 41: 162-4.
18. Harrad J, Howell P. General anaesthesia for caesarean section. Curr Anaesth Crit Care 2000; 11: 66-72. [CrossRef]
19. Dahlgren G, Granath F, Pregner K, Rösblad PG, Wessel H, Irestedt L. Colloid vs. crystalloid preloading to prevent maternal hypotension during spinal anesthesia for elective cesarean section. Acta Anaesthesiol Scand 2005; 49: 1200-6. [CrossRef]
20. Gregg AR, Weiner CP. "Normal" umbilical arterial and venous acid-base and blood gas values. Clin Obstet Gynecol 1993; 36: 24-32. [CrossRef]
21. American Academy of Pediatrics, American College of Obstetricians and Gynecologists. Neonatal encephalopathy and cerebral palsy: defining the pathogenesis and pathophysiology. Elk Grove Village (IL): AAP; Washington, DC: ACOG; 2003.
22. Bax M, Nelson KB. Birth asphyxia: A statement. World Federation of Neurology Group. Dev Med Child Neurol 1993; 35: 1022-4. [CrossRef]
23. Low JA, Lindsay BG, Derrick EJ. Threshold of metabolic acidosis associated with newborn complications. Am J Obstet Gynecol 1997; 177: 1391-4. [CrossRef]
24. Handley-Derry M, Low JA, Burke SO, Waurick M, Killen H, Derrick EJ. Intrapartum fetal asphyxia and the occurrence of minor deficits in 4- to 8-year-old children. Dev Med Child Neurol 1997; 39: 508-14. [CrossRef]
25. Morrell MJ. Reproductive and metabolic disorders in women with epilepsy. Epilepsia 2003; 44 (Sup 4): 11-20.
26. Sabers A, aRogvi-Hansen B, Dam M, Fischer-Rasmussen W, Gram L, Hansen M, et al. Pregnancy and epilepsy: A retrospective study of 151 pregnancies. Acta Neurol Scand 1998; 97: 164-70. [CrossRef]

Postpartum urinary retention after vaginal delivery: Assessment of risk factors in a case-control study

Sabri Cavkaytar, Mahmut Kuntay Kokanalı, Ayşegül Baylas, Hasan Onur Topçu, Bergen Laleli, Yasemin Taşçı

Department of Obstetrics and Gynecology, Dr. Zekai Tahir Burak Woman's Health Education and Research Hospital, Ankara, Turkey

Abstract

Objective: To assess the obstetrics risk factors for postpartum urinary retention after vaginal delivery.

Material and Methods: Of 234 women with a vaginal delivery, 19 (8.1%) women who had postpartum urinary retention were cases, and 215 (91.9%) women who did not were controls. Postpartum urinary retention was defined as the presence of postvoid residual bladder volume ≥150 mL or the inability to void within 6 hours after vaginal delivery. Logistic regression analysis identified risk factors for urinary retention.

Results: Prolonged duration of the second stage of labor (OR=0.46, 95% CI for OR=0.06-3.67, p<0.001), presence of episiotomy (OR=0.07, 95% CI for OR=0.01-0.68, p=0.022) and perineal laceration (OR=97.09, 95% CI for OR=7.93-1188.93, p<0.001), and birth weight of >4000 g for the newborn (OR=0.04, 95% CI for OR=0.01-0.20, p<0.001) were found as independent risk factors for postpartum urinary retention after vaginal delivery.

Conclusion: Postpartum urinary retention after vaginal delivery is a relatively common condition. Awareness of risk factors, including prolonged second stage of labor, episiotomy, perineal lacerations, and macrosomic birth, may allow us to take the necessary precautions against this complication. (J Turk Ger Gynecol Assoc 2014; 15: 140-3)

Key words: Bladder, delivery, risk factors, urinary retention

Received: 31 May, 2014 **Accepted:** 14 July, 2014

Introduction

Postpartum urinary retention (PPUR) is an upsetting condition that has no standard literature definition. It has been variably defined as the abrupt onset of aching or acheless inability to completely micturate, requiring urinary catheterization, over 12 h after giving birth (1) or not to void spontaneously within 6 h of vaginal delivery (2-4). In 2001, Calgary Health Region's Policy and Procedures outlined acute urinary retention as the catheterization of the bladder within the first 24 h postpartum for not voiding within 6 h postpartum, to micturate often in small amounts, or to have an urge to micturate but can not or to be catheterized for any reason for an amount of 500 mL output within the first 24 h postpartum (5). One year later, the presence of painful, palpable, or percussible bladder in a patient who is unable to pass any urine was the new definition of acute urinary retention, changed by the International Continence Society (6). Because of this disagreement, and as asymptomatic cases often remain undiagnosed, the exact incidence of PPUR is unknown. However, in the literature, the estimated incidence of PPUR varies between 0.05% and 37 % (7).

Postpartum urinary retention has been classified into overt and covert retention by Yip et al. (3). Women who are unable to micturate spontaneously within 6 h after vaginal delivery are categorized as having overt (symptomatic) urinary retention. Covert (asymptomatic) urinary retention is defined as having a postvoid residual bladder volume (PVRBV) of more than 150 mL, detected by ultrasound or by catheterization, with no symptoms of urinary retention.

The precise pathophysiology of PPUr is still unknown; however, it is likely to be multifactorial, including physiological, neurological, and mechanical processes in the postpartum period (7). Inappropriate or delayed diagnosis and management of PPUR can lead to bladder dysfunction, urinary tract infection, and catheter-related complications (8).

Detection of patients who are at risk for developing PPUR might prevent PPUR and its complications. Thus, we aimed to assess the obstetric risk factors that can predict the occurrence of PPUR in women who delivered vaginally.

Material and Methods

This case-control study was conducted in Dr. Zekai Tahir Burak Woman's Health Education and Research Hospital between January 2014 and April 2014. The study was approved by the institutional review board; 234 consecutive women who delivered term singletons vaginally after uncomplicated pregnancies were included. All participants gave informed consent.

Address for Correspondence: *Mahmut Kuntay Kokanalı, Department of Obstetrics and Gynecology, Dr. Zekai Tahir Burak Woman's Health Education and Research Hospital, Ankara, Turkey. Phone: +90 505 242 95 76 e.mail: kuntaykokanali@gmail.com*

DOI:10.5152/jtgga.2014.13102

Immediately after the first micturition in the postpartum period, all of the women underwent a transabdominal ultrasound (Mindray model DC7) to estimate PVRBV. The transducer was located in the midline on the top of the symphysis pubis to obtain the longitudinal and transverse scan of the bladder. The widest diameter in the transverse scan in cm (D1), the anteroposterior diameter in longitudinal scan in cm (D2), and the cephalocaudal diameter in the longitudinal scan in cm (D3) were recorded. Estimated PVRBV was calculated by using the formula D1×D2×D3×0.7 (9).

Women in whom the estimated PVRBV ≥150 mL or who were unable to micturate within 6 hours after vaginal delivery were defined as the cases. Women who had an estimated PVRBV<150 mL were defined as the controls.

For all participants, maternal and neonatal demographic characteristics (such as age, parity, body mass index (BMI) of the woman, birth weight, head circumference measurement of newborn); gestational age at onset of labor; use of oxytocin and analgesia; duration of the first, second, and third stage of labor; fundal pressure during the second stage of labor; macrosomic delivery (birth weight >4000 g); perineal laceration; episiotomy; and postpartum urinary symptoms (dysuria, frequent urge to urinate without being able to pass much urine, and feeling like bladder not completely empty) were collected.

Statistical analysis was performed using the Statistical Program for Social Sciences (SPSS, Version 15.0; Chicago, IL, USA). The normal distribution of the variables was analyzed by the Kolmogorov-Smirnov test. Continuous variables with normal distribution are presented as mean±standard deviation. Median (minimum-maximum) value was used where a normal distribution was absent. Quantitative variables are given as number (percentage). Statistical comparison was carried out by chi-square ($\chi 2$), Mann-Whitney U- and independent sample t-tests where appropriate. Logistic regression model was performed to analyze risk factors for PPUR. P<0.05 was considered statistically significant.

Results

Among 234 consecutive women recruited in our study, 19 women had PPUR, with an overall incidence of 8.1%. Of these 19 cases, 18 (7.7%) were covert (asymptomatic) retention, and 1 (0.4%) was overt (symptomatic) retention.

The characteristics of women and newborns are listed in Table 1. There was no significant difference regarding maternal age, gravidity, parity, BMI, gestational period, time between birth to first void, postpartum urinary symptoms of women, and head circumference of newborns between cases and controls. However, the mean birth weight of newborns for cases was statistically significantly heavier than the controls (3745.79±432.18 grams vs. 3493.63±492.68 grams, p<0.032). Also, the mean PVRBV of cases was significantly higher than controls (202.11±60.15 mL vs. 57.84±26.63 mL, p<0.001).

With respect to obstetric characteristics, there were no significant differences in duration of the first stage (714. 21±44.10 minutes vs. 693.26±65.20 minutes, p=0.171) and the third stage of labor (4.74±0.45 minutes vs. 4.79±2.83 minutes, p=0.934) between cases and controls, respectively. But, the mean duration of the second stage of labor was statistically significantly longer in cases as compared to controls (38.42±9.44 minutes vs. 23.00±11.72 minutes, p<0.001). Chi-square test showed that cases and controls were similar with regard to incidence of labor induction with intravenous oxytocin (p=0.811) or analgesia use during labor (p=0.636). However, the incidence of fundal pressure during the second stage of labor, macrosomic newborn, episiotomy, and perineal laceration were more common in cases than in controls (Table 2).

Table 1. Characteristics of women and newborns

	Cases (n=19)	Controls (n=215)	p*
Maternal Age (years)	27.79±7.18	26.38±5.93	0.331
Gravidity	1 (1-3)	2 (1-4)	0.475
Parity	1 (0-2)	1 (0-3)	0.723
Body Mass Index (kg/m^2)	26.24±1.47	26.07±1.57	0.646
Gestational period (days)	267.74±8.96	267.56±7.46	0.924
Birth weight (grams)	3745.79±432.18	3493.63±49268	0.032
Head circumference (cm)	50.00±0.94	49.96±0.96	0.871
Time birth to the first void (hours)	3.93±1.61	3.11±1.09	0.042
PVRBV (mL)	202.11±60.15	57.84±26.63	<0.001
Postpartum urinary symptoms	4 (21.1)	31 (14.4)	0.498

Data were presented as mean±standard deviation, median (minimum-maximum and number (%)
PVRBV: postvoid residual bladder volume
*p<0.05 was considered statistically significant.

When we examined the potential risk factors for PPUR by logistic regression model (Table 3), parity, use of analgesia during labor, duration of the first stage of labor, labor induction with intravenous oxytocin, fundal pressure during the second stage of labor, and time between birth to first void were not significantly related to PPUR. Prolonged duration of the second stage of labor (W=16.13, OR=0.46, 95% CI for OR=0.06-3.67, p<0.001), presence of episiotomy (W=5.25, OR=0.07, 95% CI for OR=0.01-0.68, p=0.022), perineal laceration repair (W=12.81, OR=97.09, 95% CI for OR=7.93-1188.93, p<0.001), and birth weight of >4000 g for the newborn (W=13.99, OR=0.04, 95% CI for OR=0.01-0.20, p<0.001) were significant risk factors to predict PPUR after vaginal delivery.

Discussion

In our study, PPUR after vaginal delivery was found as a relatively common occurrence, with an incidence of 8.1% (19/234). In the literature, the incidence of PPUR varies widely (10, 11). But, the estimated incidence is likely to be more, since most cases often remain unforeseen. Overt retention is easily detected, while covert retention is identified only by ultrasound or by catheterization, since most women give no symptoms.

Table 2. Obstetrics characteristics

	Cases (n=19)	Controls (n=215)	p*
Duration of the first stage (min)	714.21±44.10	693.26±65.20	0.171
Duration of the second stage (min)	38.42±9.44	23.00±11.72	<0.001
Duration of the third stage (min)	4.74±0.45	4.79±2.83	0.934
Labor induction with IV oxytocin	8 (42.1)	103 (47.9)	0.811
Analgesia during labor	10 (52.6)	99 (46.0)	0.636
Fundal pressure	9 (47.4)	44 (20.5)	0.018
Macrosomic newborn	8 (42.1)	13 (6.0)	<0.001
Episiotomy	15 (78.9)	102 (47.4)	0.015
Perineal laceration	13 (68.4)	49 (22.8)	<0.001

Data were presented as mean±standard deviation and number (%).
*p<0.05 was considered statistically significant.

Table 3. Logistic regression analysis of risk factors for PPUR

	Wald	p*	OR	95% CI for OR
Parity	0.54	0.461	0.46	0.06-3.67
Analgesia during labor	0.77	0.381	0.97	0.89-1.05
Duration of the first stage	0.29	0.591	0.53	0.05-5.31
Duration of the second stage	16.13	<0.001	0.89	0.84-0.94
Labor induction with IV oxytocin	0.01	0.983	0.99	0.46-2.14
Fundal pressure	0.71	0.247	0.44	0.11-1.78
Episiotomy	5.25	0.022	0.07	0.01-0.68
Perineal laceration	12.81	<0.001	97.09	7.93-1188.93
Macrosomic newborn	13.99	<0.001	0.04	0.01-0.20
Time from birth to the first void	1.96	0.161	8.88	0.42-188.19

OR: odds ratio; CI: confidence interval; PPUR: postpartum urinary retention
*p<0.05 was considered statistically significant

In the literature, many different obstetrical risk factors have been considered for the pathogenesis of PPUR; however, the exact etiology of PPUR has not been clearly identified. The incidence of PPUR has been found to be higher in primigravidae than in multigravidae (10, 12). In the present study, however, parity was not a risk factor for PPUR. A high incidence of PPUR was reported in patients with regional anesthesia (12, 13) and instrument-assisted vaginal delivery (14). But, in our study, there were no women who had regional analgesia or instrumental delivery. In a retrospective analysis of 11,108 vaginal deliveries by Pifarotti et al. (15), PPUR was detected in 105 women, and fundal pressure during the second stage of labor was an important risk factor for the development of PPUR. In our current study, although fundal pressure was statistically more common among the cases than among the controls, it was not found as an effective factor for PPUR in the regression analysis model.

We identified that a prolonged second stage of labor and delivery of macrosomic newborn were the risk factors associated with the occurrence of PPUR. Similarly, Kekre et al. (16) reported that the lengths of the first and second stages of labor were directly related to postpartum urine residual volume, and labor duration ≥700 min was also associated with a greater incidence of PPUR. It is possible that mechanical strength applied to the pelvic muscle floor during prolonged second stage of labor, in addition to the rise in abdominal pressure with a macrosomic baby, may contribute to pelvic and pudendal nerve damage, resulting in neurologic impairment of micturition and, therefore, urinary retention.

We also found that the PPUR incidence was higher in women who had perineal lacerations and episiotomy than in women who had none. Although, episiotomy, birth canal injury, and severe perineal lacerations were reported as being related to increased risk of urinary retention in some studies (10, 17), in a recent cross-sectional study, these factors were not found to be effective in developing PPUR (16). However, we think that the pain caused by the repair of episiotomy or lacerations might result in reflex urethral spasm, and PPUR occurs subsequently. Postpartum urinary retention can damage detrusor muscles and parasympathetic nerves of the bladder wall and change detrusor function, as well. Also, increased levels of progesterone during pregnancy and the early puerperium period might cause bladder atony and facilitate detrusor damage (12, 18, 19). If any delay or misdiagnosis of PPUR occurs, the damage can be irreversible. Thus, early diagnosis and appropriate treatment approaches have great importance. An indwelling catheter can be used for 2 or 3 days if the woman is unable to void; in cases of persistent PVRBV of more than 150 mL, an intermittent clean catheterization is applied until the PVRBV is less than 150 mL (16).

According to the RCOG Incontinence in Women Study Group, every postdelivery woman should void within 6 hours; if not, catheterization should be performed (20). Also, both the NICE guideline on Postnatal Care and the WHO Technical Consultation on Postpartum and Postnatal Care state that if there is no voiding within 6 hours of birth and the struggle of voiding methods is not successful, the bladder volume should be assessed, and catheterization should be considered (21, 22). Although ultrasonographic measurement of PVRBV in the postpartum patient is doubtful, due to postpartum uterine size (7), several authors (23, 24) offer assessment of the bladder accurately by ultrasound, even in the postpartum period. In a recent review including 24 studies, it was concluded that a standard treatment guideline for PPUR is necessary, since there is no sufficient evidence about the catheterization methods for overt PPUR (25). In the same review, it was recommended that both overt and covert PPUR should be regarded as serious conditions. Routine use of bladder scanning by ultrasonography in the early postpartum period may be beneficial. Future studies investigating the cost-effectiveness and advantages of routine postpartum bladder scanning are needed.

In conclusion, PPUR is a relatively common condition that can cause irreversible damage to bladder function. Longer second stage of labor, delivery of a macrosomic newborn, the presence of perineal lacerations, and episiotomy are significant risk factors for the development of PPUR. Awareness of risk factors may allow the obstetrician to prevent this complication. Further studies with more participants are needed to identify the exact etiology of PPUR and to clarify whether routine postpartum bladder scanning is cost-effective and beneficial.

Ethics Committee Approval: *Ethics committee approval was received for this study from the ethics committee of Zekai Tahir Burak Education and Research Hospital.*

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

Peer-review: *Externally peer-reviewed.*

Author contributions: *Concept - S.C., M.K.K.; Design - S.C., M.K.K.; Supervision - Y.T.; Resource - A.B., H.O.T., B.L.; Materials - A.B., B.L.; Data Collection&/or Processing - A.B., B.L.; Analysis&/or Interpretation - S.C., M.K.K., H.O.T.; Literature Search - S.C., M.K.K., H.O.T.; Writing - S.C., M.K.K.; Critical Reviews - Y.T.*

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

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

References

1. Ramsay IN, Torbet TE. Incidence of abnormal voiding parameter in the immediate postpartum period. Neurourol Urodyn 1993; 12: 179-83. [CrossRef]
2. Andolf E, Fosif CS, Jorgensen C, Rydhstrom H. Insidious urinary retention after vaginal delivery: Prevalence and symptoms at follow-up in a population-based study. Gynecol Obstet Invest 1994; 38: 51-3. [CrossRef]
3. Yip SK, Brieger G, Hin LY, Chung T. Urinary retention in the postpartum period: The relationship between obstetrics factors and the postpartum post-void residual bladder volume. Acta Obstet Gynaecol Scand 1997; 76: 667-72. [CrossRef]
4. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. Standardization of terminology of lower urinary tract function: Report from the standardization subcommittee of the International Continence Society. Neurourol Urodyn 2002; 21: 167-78. [CrossRef]
5. Calgary Health Region. Bladder care/fluid balance: Intrapartum and postpartum. Women's and Infant Health Policies and Procedures manual. 2001.
6. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Urology 2003; 61: 37-49. [CrossRef]
7. Lim JL. Post-partum voiding dysfunction and urinary retention. Aust N Z J Obstet Gynaecol 2010; 50: 502-5. [CrossRef]
8. Zaki MM, Pandit M, Jackson S. National survey for intrapartum and postpartum bladder care: Assessing the need for guidelines. BJOG 2004; 111: 874-6. [CrossRef]
9. Poston GJ, Joseph AEA, Riddle PT. The accuracy of ultrasound in the measurement of changes in bladder volume. Br J Urol 1983; 55: 361-3. [CrossRef]
10. Caley ME, Caley JM, Vasdey G, Lesnick TG, Webb MJ, Ramin KD, et al. Factors that are associated with clinically overt postpartum urinary retention after vaginal delivery. Am J Obstet Gynecol 2002; 187: 430-3. [CrossRef]
11. Lee SNS, Lee CP, Tang OSF, Wong WM. Postpartum urinary retention. Int J Urogynaecol Obstet 1999; 66: 287-8. [CrossRef]
12. Liang CC, Chang SD, Chang YL, Chen SH, Chueh HY, Cheng PJ. Postpartum urinary retention after cesarean delivery. Int J Gynecol Obstet 2007; 99: 229-32. [CrossRef]
13. Ching-Chung L, Shuenn-Dhy C, Ling-Hong T, Ching C, Chao-Lun C, Po-Jen C. Postpartum urinary retention: assessment of contributory factors and long term clinical impact. Aust NZ J Obstet Gynecol 2002; 42: 365-8. [CrossRef]
14. Yip SK, Sahota D, Pang MW, Chang A. Postpartum urinary retention. Acta Obstet Gynecol Scand 2004; 83: 881-91. [CrossRef]
15. Pifarotti P, Gargasole C, Folcini C, Gattei U, Nieddu E, Sofi G, et al. Acute post-partum urinary retention: analysis of risk factors, a case-control study. Arch Gynecol Obstet 2014; 289: 1249-53. [CrossRef]
16. Kekre AN, Vijayanand S, Dasgupta R, Kekre N. Postpartum urinary retention after vaginal delivery. Int J Gynaecol Obstet 2011; 112: 112-5. [CrossRef]
17. Liang CC, Wong SY, Tsay PT, Chang SD, Tseng LH, Wang MF, Soong YK. The effect of epidural analgesia on postpartum urinary retention in women who delivery vaginally. Int J Obstet Anesth 2002; 11: 164-9. [CrossRef]
18. Groutz A, Hasson J, Gold R, Pauzner D, Lessing J, Gordon D. Persistent postpartum urinary retention: prevalence, obstetrics risk factors and management. J Urol 2008; 179 (4 Suppl): S472. [CrossRef]
19. Jeffery TJ, Thyer B, Tsokos N, Taylor JD. Chronic urinary retention postpartum. Aust N Z J Obstet Gynaecol 1990; 30: 364-6. [CrossRef]
20. MacLean AB, Cardozo L, eds. Incontinence in Women - Study Group Statement. London: Royal College of Obstetricians and Gynaecologists Press; 2002. p. 433-41.
21. Routine Postnatal Care of Women and their Babies. National Institute for Health and Clinical Excellence Guideline 37. London; 2006.
22. World Health Organization. World Health Organization Technical Consultation on Postpartum and Postnatal Care. Geneva: World Health Organization; 2010.
23. Yip SK, Sahota D, Chang A. Determining the reliability of ultrasound measurements and the validity of the formulae for ultrasound estimation of postvoid residual bladder volume in postpartum women. Neurourol Urodyn 2003; 22: 255-60. [CrossRef]
24. Demaria F, Amar N, Biau D, et al. Prospective 3D ultrasonographic evaluation of immediate postpartum urinary retention volume in 100 women who delivered vaginally. Int Urogynecol J Pelvic Floor Dysfunct 2004; 15: 281-5.
25. Mulder FE, Hakvoort RA, Schoffelmeer MA, Limpens J, Van der Post JA, Roovers JP. Postpartum urinary retention: A systematic review of adverse effects and management. Int Urogynecol J 2014 May 20. [Epub ahead of print]

Obesity is not associated with the poor pregnancy outcome following intracytoplasmic sperm injection in women with polycystic ovary syndrome

Funda Akpınar, Berfu Demir, Serdar Dilbaz, İskender Kaplanoğlu, Berna Dilbaz

Department of In Vitro Fertilization, Etlik Zübeyde Hanım Maternity & Women's Health Teaching Research Hospital, Ankara, Turkey

Abstract

Objective: To determine if body mass index has an effect on the outcome of *in vitro* fertilization in patients with polycystic ovary syndrome undergoing controlled ovarian hyperstimulation.

Material and Methods: The study included 337 cycles. Patients were stratified into the following 3 groups: normal weight, overweight, and obese. The primary outcome measures were response to ovarian hyperstimulation, the fertilization rate, the implantation rate, and the clinical and ongoing pregnancy rates.

Results: Total gonadotropin consumption increased, and the number of retrieved oocytes decreased as the body mass index increased. The implantation rate and clinical pregnancy rate were similar in all 3 groups. In response to the mid-luteal long protocol, the cycle cancellation rate was lower and the number of retrieved oocytes was higher in the overweight and obese groups, as compared to the antagonist protocol.

Conclusion: The body mass index did not affect the outcome of *in vitro* fertilization in women with polycystic ovary syndrome. Additional research is required to better understand the role of stimulation protocols on the cycle outcome. (J Turk Ger Gynecol Assoc 2014; 15: 144-8)

Key words: *In vitro* fertilization, polycystic ovary syndrome, body mass index

Received: 07 May, 2014 **Accepted:** 01 July, 2014

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age (1, 2). High luteinizing hormone and androgen levels in PCOS have a detrimental effect on oocyte maturity and fertilization (3) and are associated with a decrease in the pregnancy rate and an increase in the miscarriage rate (4). In addition, PCOS patients undergoing *in vitro* fertilization (IVF) have a high risk of ovarian hyperstimulation syndrome (OHSS) - an iatrogenic complication of controlled ovarian hyperstimulation (COH) (5).

Obesity is an epidemic that is affecting more women of reproductive age every year (6). Some IVF studies have reported that obesity is associated with the need for higher gonadotropin doses, an increase in the cycle cancellation rate, lower oocyte yield, and an increase in the miscarriage rate (7-9), whereas others have not noted any negative effects of obesity on IVF outcome (10, 11).The discrepancy in findings might be due to differences in the degree of obesity analyzed, stimulation protocols, and causes of infertility, and the overlapping features of PCOS and obesity, which makes it difficult to determine which factors affect IVF outcome (12, 13).

The primary aim of the present study was to investigate the effect of body mass index (BMI) on the outcome of IVF via intracytoplasmic sperm injection (ICSI) in women with PCOS. The study's secondary aim was to determine if there are any differences in cycle performance associated with the mid-luteal long gonadotropin releasing hormone (GnRH) agonist and flexible GnRH antagonist protocols in PCOS patients according to BMI.

Material and Methods

Data stored in a computer database on women with PCOS that underwent IVF treatment between May 2007 and August 2012 were retrospectively analyzed. The study protocol was approved by the Etlik Zübeyde Hanim Training and Research Institutional Review Board and written informed consent was obtained from the patients related to the treatment procedure. The study cohort consisted of PCOS patients that met the following criteria: BMI of 18.5-35 kg m^{-2}; undergoing ovarian stimulation using the mid-luteal long GnRH agonist protocol or the flexible GnRH antagonist protocol; and age ≤35 years. Women that underwent freeze-thaw cycles were excluded. All participants were stratified into 3 BMI groups according to the World Health Organization (WHO) classification system for obesity (14): normal weight (BMI: 18.5-24.9 kg m^{-2} [group 1]); overweight (BMI: 25-29.9 kg m^{-2} [group 2]); and obese (BMI: 30-34.9 kg m^{-2} [group3]).

Patients treated with the mid-luteal long GnRH agonist protocol took an oral contraceptive pill (Desolett; Schering Plough Medical, İstanbul, Turkey) for 21 d starting on d 3 of spontaneous menses. The gonadotropin starting dose ranged from 75 IU to 300 IU based on BMI. On d 16, daily GnRH agonist

Address for Correspondence: *Funda Akpınar, Department of In Vitro Fertilization, Etlik Zübeyde Hanım Maternity & Women's Health Teaching Research Hospital, Ankara, Turkey. Phone: +90 533 564 77 81 e.mail: fundaakpinar@yahoo.com*

DOI:10.5152/jtgga.2014.13047

Table 1. Demographic characteristics of groups

Variable	Group 1 (n=109)	Group 2 (n=84)	Group 3 (n=79)	p value
No. of patients	84	59	50	
Age (years)	28.1±4.6	29.0±3.9	29.2±4.2	NS
Hormone Profile				
FSH (IU/L)	5.9±1.7	5.9±1.4	5.4±1.3	NS
LH (IU/L)	8.6±6.0[a]	7.6±4.7	5.9±2.9	.006
E2 (pg/mL)	43.6±19.4[b]	37.0±14.1	40.4±13.2	.043
Antral follicle count	18.7±7.5	18.6±5.9	18.1±6.2	NS
Type of infertility				NS
Primary	87 (79.8%)	69 (82.1%)	56 (70.9%)	
Secondary	22 (20.2%)	15 (17.9%)	23 (29.1%)	
Duration of infertility (months)	68.8±44.2[a,b]	91.2±49.9	100.4±51.6	≤.001
Number of previous IVF cycles	1.6±1.0	1.6±1.0	1.8±1.1	NS
Causes of infertility				
Male factor	54 (49.5%)[b]	31 (36.9%)	25 (31.6%)	.035
Tuboperitoneal	4 (3.7%)	6 (7.1%)	-	
Ovulatory dysfunction	91 (83.5%)	69 (82.1%)	65 (82.3%)	NS
Unexplained	44 (40.4%)	41 (48.8%)	39 (49.4%)	NS

[a]: Group 1 vs Group 2 (p<.05). [b]: Group 1 vs Group 3 (p<.05). Data are expressed as mean±SD.
No: number; FSH: follicle-stimulating hormone; LH: luteinizing hormone; E2: estradiol; IVF: *in vitro* fertilization

(Lucrin; Abbott Laboratories, İstanbul, Turkey) was initiated until human chorionic gonadotropin (hCG) administration. On d 3 of the next menstruation, gonadotropin stimulation was initiated. Patients treated with the flexible GnRH antagonist protocol started gonadotropin stimulation on d 3 of spontaneous menses (starting dose of 75-300 IU based on BMI). Then, GnRH antagonist (Orgalutran; Schering Plough Medical, İstanbul, Turkey) was started when a follicle was >13 mm and/or E2 >250 pg/mL^{-1}.

Ovarian response was monitored via transvaginal ultrasound (Mindray DC-T6; Shenzhen, China) and serum estradiol measurement. When ≤3 lead follicles with a mean diameter >17 mm were measured, 250 μg of hCG (Ovitrelle; Merck Serono Medical, İstanbul, Turkey) was administered subcutaneously for final oocyte maturation. Oocyte retrieval was performed under general anesthesia and transvaginal ultrasound (Mindray DC-T6; Shenzhen, China) guidance 35.5 h after administration of hCG. Patients were considered high risk for OHSS if they had any of the following: serum estradiol level ≥5000 ng/L^{-1}on the day of hCG administration and retrieval of ≥18 follicles and/or a BMI <24 kg m^{-2}. To prevent OHSS in the high-risk patients cabergoline 0.25 mg once daily per oral (Dostinex; Pfizer, Ascoli Piceno, Italia) was initiated on the day of hCG administration and continued until the day of embryo transfer, and colloid of hydroxyethyl starch (Voluven; Fresenius Kabi, İstanbul, Turkey) was intravenously administered at the time of oocyte retrieval. ICSI was routinely performed with all oocytes. Embryo transfer was performed on d 3 or 5 after retrieval, based on the number and quality of embryos. Embryos were evaluated 40-45 h and 65-70 h after ICSI for cleavage stage and were scored according to previously reported embryo evaluation criteria as the number and quality of blastomeres, the percentage of fragmentation, and the existence of a multinucleus (15). Blastocyst-stage embryos were scored according to the expansion of the blastocyst and the structure of the inner cell mass and trophectoderm (15). Embryo transfer was performed using a soft catheter (Wallace; Smiths Medical, Dublin, USA) under transabdominal ultrasound guidance (Mindray DC-T6; Shenzhen, China).

All patients received luteal support with vaginal progesterone gel (Crinone gel 8%; Serono Medical, Istanbul, Turkey) t.i.d. beginning the day of oocyte retrieval. Serum βhCG levels were measured 12 d after embryo transfer. Severe OHSS was considered the development of OHSS (16) with hematocrit >45%, WBC count >15,000 mm^{-3}, electrolyte imbalance, elevated liver enzymes, and a serum creatinine level >1.2 mg/dL^{-1}.

Data analysis was performed using SPSS v. 11.5 for Windows (SPSS, Inc., Chicago, IL, USA). The Shapiro-Wilk test was used to determine if the distribution of continuous variables was normal or not. Levene's test was used to evaluate the homogeneity of variances. Data are shown as mean±SD or median (range), where applicable. Nominal data are expressed as n and percentage. Mean differences between groups were compared via one-way ANOVA, and the Kruskal-Wallis test was used to compare median values. When the P value for one-way ANOVA or Kruskal-Wallis test results was statistically significant, post hoc Tukey's HSD or Conover's non-parametric multiple comparison tests, respectively, was used to determine which groups

Table 2. Cycle outcomes of groups

Variable	Group 1 (n=109)	Group 2 (n=84)	Group 3 (n=79)	p value
No. of patients	84	59	50	
Cycle cancellation n (%)	2 (1.8%)	5 (6.0%)	2 (2.5%)	NS
Poor response	2 (1.8%)	1 (1.2%)	2 (2.5%)	NS
OHSS	-	2 (2.4%)	-	NS
Follicular discordance	-	2 (2.4%)	-	NS
Stimulation protocol n (%)				NS
Midluteal long GnRH agonist	83 (76.1%)	55 (65.5%)	61 (77.2%)	
Flexible GnRH antagonist	26 (23.9%)	29 (34.5%)	18 (22.8%)	
Duration of stimulation (days)	9.9±2.3	9.6±2.4	10.4±2.9	NS
Total gonadotropin dose (IU)	1558.6±632.0[a,b]	1731.0±657.6[c]	2094.6±796.9	≤.001
Mean progesterone level on the day of HCG	1.6±1.0	1.6±1.0	1.8±1.1	NS
Estradiol level on the hCG day (pg/mL)	3240.1±1857.0[b]	2813.3±1621.0[c]	2287.4±1333.6	≤.001
Endometrial thickness on hCG day (mm)	10.3±2.3	9.6±2.3	9.7±2.1	NS
No. of total oocytes	17.6±9.0[b]	16.8±8.1[c]	13.8±7.1	.015
No. of mature oocytes	12.7±6.6[b]	11.8±6.8	9.5±5.2	.008
No. of G1 embryo	1.25±1.04[b]	1.25±1.00[c]	1.64±1.03	.035
Severe OHSS	8 (7.3%)[b]	5 (6.0%)	0 (0%)	.009

[a]: Group 1 vs Group 2 (p<.05). [b]: Group 1 vs Group 3 (p<.05). [c]: Group 2 vs Group 3 (p<.05) . Data are expressed as mean±SD.
No: number; OHSS: ovarian hyperstimulation syndrome; GnRH: gonadotropin-releasing hormone; hCG: human chorionic gonadotropin; G1: Grade 1

differed from each other. Nominal data were analyzed using Pearson's chi-square or Fisher's exact test, where applicable. The level of statistical significance was set at $p<0.05$.

Results

In total, 337 cycles in 193 PCOS patients were analyzed. Patient baseline characteristics, including age, basal hormone profile, antral follicle count, type of infertility, number of previous IVF cycles, and cause of infertility, were similar in all 3 groups (Table 1). The response to COH in each group is shown in Table 2. Total gonadotropin consumption was highest in group 3, followed by group 2 (group 3 vs. group 2: $p=0.004$; group 3 vs. group 1: $p<0.001$; group 2 vs. group 1: $p=0.022$). The estradiol level on the day of hCG administration was lower in group 3 than in group 2 and group 1 (group 3 vs. group 2: $p=0.029$; group 3 vs. group 1: $p<0.001$). The number of oocytes retrieved was lower in group 3 than in group 2 and group 1 (group 3 vs. group 2: $p=0.017$; group 3 vs. group 1: $p=0.005$). The number of mature oocytes was lower in group 3 than in group 1 ($p<0.001$). None of the patients in group 3 had severe OHSS, as compared to 8 patients in group 1; the difference was significant ($p=0.022$).

Cycle performance and pregnancy outcome in group 1 were similar for those treated with the mid-luteal long GnRH agonist and flexible GnRH antagonist protocols. In group 2, the cycle cancellation rate and duration of stimulation were significantly higher in those that received the flexible GnRH antagonist protocol, as compared to the mid-luteal long GnRH agonist protocol ($p=0.004$ and $p=0.016$, respectively). In group 3, the number of oocytes and number of mature oocytes were significantly higher in those that received the mid-luteal long GnRH agonist protocol, as compared to the flexible GnRH antagonist protocol ($p=0.01$ and $p=0.01$, respectively). Pregnancy outcomes associated with both protocols were similar in all 3 groups (Table 3).

Discussion

Obesity and PCOS are closely related disorders with overlapping features (17), including a possible negative effect on the outcome of ICSI. The present study aimed to determine the effect of BMI on the outcome of ICSI in women with PCOS. The present findings show that PCOS patients in the normal weight group (Group 1) had the best cycle outcomes; however, the pregnancy rate in Group 1 and Group 3 (obese group) was similar.

Age of the female is the most important factor associated with IVF success. Regardless of BMI, as female age increases the risk for poor IVF outcome increases. Age-related decline in oocyte quality and the IVF fertilization rate is well documented; as such, maximum age in the present study was restricted to 35 years.

A significant association was observed in the present study between BMI and gonadotrophin requirement, which is in agreement with earlier reports of "gonadotrophin resistance" (7, 8, 11, 13, 18). Gonadotrophin resistance in obesity could be related to the volume of distribution or peripheral metabolic clearance.

Table 3. Cycle and pregnancy outcomes of the groups according to protocol

Variable	Group 1 (n=109)			Group 2 (n=84)			Group 3 (n=79)		
	Agonist (n=83)	Antagonist (n=26)	p	Agonist (n=55)	Antagonist (n=29)	p	Agonist (n=61)	Antagonist (n=18)	p
Cycle cancellation n (%)	2 (2.4%)	0 (0%)	NS	0 (0%)	5 (17.2%)	.004	2 (3.3%)	0 (0%)	NS
Duration of stimulation (days)	9.5±1.9	10.8±2.9	NS	9.2±2.4	10.3±2.0	.016	10.3±3.0	10.5±2,4	NS
Total gonadotropin dose (IU)	1567.0±574.3	1532.8±798.1	NS	1727.8±663.6	1738.1±657.8	NS	2109.6±833.5	2044.4±679.3	NS
No. of total oocytes	18.4±9.4	15.4±7.6	NS	16.3±7.4	18.0±9.6	NS	14.9±7.3	10.1±4.7	.010
No. of mature oocytes	13.5±6.6	10.5±6.3	NS	11.5±6.2	12.6±8.0	NS	10.4±5.3	6.6±4.2	.010
Severe OHSS	6 (7.2%)	2 (7.7%)	NS	4 (7.3%)	1 (3.4%)	NS	0 (0%)	0 (0%)	NS
Fertilization rate (%)	44.5±21.5	41.1±22.6	NS	42.4±19.7	44.7±24.2	NS	48.3±23.5	40.2±30.9	NS
Implantation rate/ET (%)	36 (54.5%)	11 (44.0%)	NS	26 (51.0%)	10 (50.0%)	NS	19 (38.8%)	5 (41.7%)	NS
Biochemical pregnancy/ET n (%)	5 (7.6%)	3 (12.0%)	NS	8 (15.7%)	2 (10.0%)	NS	6 (12.2%)	0 (0.0%)	NS
Clinical pregnancy/ET n (%)	31 (47.0%)	8 (32.0%)	NS	18 (35.3%)	8 (40.0%)	NS	13 (26.5%)	5 (41.7%)	NS
Miscarriage/ET n (%)	11 (16.7%)	2 (8.0%)	NS	6 (11.8%)	2 (10.0%)	NS	4 (8.2%)	2 (16.7%)	NS
Ongoing pregnancy/ET n (%)	20 (30.3%)	6 (24.0%)	NS	12 (23.5%)	6 (30.0%)	NS	9 (18.4%)	3 (25.0%)	NS
Multiple pregnancy/ET n (%)	8 (12.1%)	0 (0.0%)	NS	3 (5.9%)	1 (5.0%)	NS	4 (8.2%)	1 (8.3%)	NS

Data are expressed as mean±SD.
No: number; OHSS: ovarian hyperstimulation syndrome; ET: embryo transfer

Exogenous FSH was shown to course different absorption and metabolism in lean versus obese women with PCOS (19, 20).

The effect of BMI on oocyte and embryo quality remains contentious. Some studies reported poorer embryologic outcome in obese patients (12, 13, 21, 22), whereas others did not observe a similar association (7, 12, 23). Some studies indicate that adverse follicular conditions associated with insulin resistance, endocrine alterations, and possibly embryo- toxic cytokines are responsible for low embryo quality (12, 13, 21, 22), whereas others indicate that obesity-associated impaired embryo quality is only theoretical if age- and ovarian reserve-matched controls are compared (7, 11, 23). In the present study the number of grade 1 embryos was significantly higher in Group 3 (obese PCOS patients). The significantly higher LH level observed in Group 1 (normal weight) might have negatively effected oocyte quality (3, 24), resulting in a lower number of grade 1 embryos. The higher quality embryos might have resulted in a better than expected pregnancy rate in Group 3 (obese group).

In the present study patients in Group 2 (overweight) and Group 3 (obese) that received the mid-luteal long GnRH-agonist (agonist) protocol had better cycle characteristics -including a lower cycle cancellation rate- than those that received the flexible GnRH-antagonist (antagonist) protocol. Discordance of follicular growth was the primary cause of cycle cancellation in the patients that received the flexible GnRH-antagonist protocol. During the early follicular phase, early antral follicles present noticeable size heterogeneities that may be amplified during ovarian stimulation (25). Use of oral contraceptive in previous cycles in the patients that received the mid-luteal long GnRH-agonist protocol might have supplied cohort coordination. To have similar homogeneity of antral follicles in antagonist cycles luteal FSH suppression by either estrogen or GnRH antagonist administration could have been tried which we did not cross our mind due to lack of enough clinical experience in antagonist protocol. A meta-analysis by Griesinger et al. (26) that included 305 PCOS patients treated with antagonist and agonist protocols reported comparable IVF outcomes in both groups. The researchers concluded that more prospective studies are required to determine the optimal stimulation protocol based on BMI in PCOS patients.

In the present study the number of severe OHSS patients and the estradiol level on the day of hCG administration were both significantly higher in Group 1(normal weight) than in Group 3(obese). It is well known that low body weight and PCOS are risk factors for OHSS (5). In the present study obesity was observed to protect against OHSS in population of PCOS women.

The present study's retrospective design is its primary limitation. Mild and moderate OHSS cases were not included because they were treated as outpatients and they were not included in our computerized patient database. Furthermore, patients that were morbidly obese (BMI >40 kgm^{-2}, n=4) and underweight (BMI <18.5 kg m^{-2}, n=5) were not included in the analysis because of their small numbers. The prevalence of morbid obesity in Turkey

might be different than in other countries due to the potential effect of a Mediterranean diet and coincidence of PCOS and being underweight occurs with a low prevalence with insulin resistance observed in PCOS. These might result smaller sample sizes in morbid obese and underweight groups.

The number of collected oocytes in the present study was lower and the required gonadotrophin dose was higher in obese women with PCOS, but obesity was not associated with a lower pregnancy rate. Cycle performance, embryologic, and pregnancy outcomes were similar in the overweight and normal weight women with PCOS, indicating the possibility that overweight PCOS patients may be within the spectrum of normal (27), or that obesity is the cut-off point for compensatory mechanisms. Although the number of mature oocytes was higher and the cycle cancellation rate was lower in the overweight and obese patients that received the mid-luteal long GnRH-agonist protocol than in those that received the flexible GnRH-antagonist protocol, the pregnancy rate was similar for both protocols. In conclusion, additional research is required to determine the optimal stimulation protocol in PCOS patients based on BMI.

Ethics Committee Approval: *Ethics committee approval was received for this study from Etlik Zübeyde Hanim Training and Research Hospital Institutional Review Board.*

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

Peer-review: *Externally peer-revieved.*

Author contributions: *Concept - F.A., B.D., S.D.; Design - F.A., B.D., I.K.; Supervision - B.D., S.D., B.D.; Resource - B.D., S.D., I.K.; Materials - B.D., S.D., I.K.; Data Collection&/or Processing - F.A., B.D.; Analysis&/or Interpretation - F.A., B.D., S.D.; Literature Search - F.A., B.D., I.K.; Writing - F.A., B.D., S.D.; Critical Reviews - B.D., S.D., B.D.*

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

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

References

1. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 2004; 81: 19-25. [CrossRef]
2. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004; 19: 41-7. [CrossRef]
3. Tarlatzis BC, Grimbizis G, Pournaropoulos F, et al. The prognostic value of basal luteinizing hormone:follicle-stimulating hormone ratio in the treatment of patients with polycystic ovarian syndrome by assisted reproduction techniques. Hum Reprod 1995; 10: 2545-9.
4. Balen AH, Tan SL, MacDougall J, Jacobs HS. Miscarriage rates following in-vitro fertilization are increased in women with polycystic ovaries and reduced by pituitary desensitization with buserelin. Hum Reprod 1993; 8: 959-64.
5. Practice Committee of American Society for Reproductive Medicine. Ovarian hyperstimulation syndrome. Fertil Steril 2008; 90 (5 Suppl): S188-93. [CrossRef]
6. Linne Y. Effects of obesity on women's reproduction and complications during pregnancy. Obes Rev 2004; 5: 137-43. [CrossRef]
7. Fedorcsak P, Dale PO, Storeng R, et al. Impact of overweight and underweight on assisted reproduction treatment. Hum Reprod 2004; 19: 2523-8. [CrossRef]
8. Maheshwari A, Stofberg L, Bhattacharya S. Effect of overweight and obesity on assisted reproductive technology--a systematic review. Hum Reprod Update 2007; 13: 433-44. [CrossRef]
9. Rittenberg V, Seshadri S, Sunkara SK, Sobaleva S, Oteng-Ntim E, El-Toukhy T. Effect of body mass index on IVF treatment outcome: an updated systematic review and meta-analysis. Reprod Biomed Online 2011; 23: 421-39. [CrossRef]
10. Lashen H, Ledger W, Bernal AL, Barlow D. Extremes of body mass do not adversely affect the outcome of superovulation and in-vitro fertilization. Hum Reprod 1999; 14: 712-5. [CrossRef]
11. Dechaud H, Anahory T, Reyftmann L, Loup V, Hamamah S, Hedon B. Obesity does not adversely affect results in patients who are undergoing in vitro fertilization and embryo transfer. Eur J Obstet Gynecol Reprod Biol 2006; 127: 88-93. [CrossRef]
12. Jungheim ES, Lanzendorf SE, Odem RR, Moley KH, Chang AS, Ratts VS. Morbid obesity is associated with lower clinical pregnancy rates after in vitro fertilization in women with polycystic ovary syndrome. Fertil Steril 2009; 92: 256-61. [CrossRef]
13. McCormick B, Thomas M, Maxwell R, Williams D, Aubuchon M. Effects of polycystic ovarian syndrome on in vitro fertilization-embryo transfer outcomes are influenced by body mass index. Fertil Steril 2008; 90: 2304-9. [CrossRef]
14. Obesity: Preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser 2000; 894: i-xii, 1-253.
15. Baczkowski T, Kurzawa R, Głabowski W. Methods of embryo scoring in in vitro fertilization. Reprod Biol 2004; 4: 5-22.
16. Navot D, Bergh PA, Laufer N. Ovarian hyperstimulation syndrome in novel reproductive technologies: prevention and treatment. Fertil Steril 1992; 58: 249-61.
17. Cırık DA, Dilbaz B. What do we know about metabolic syndrome in adolescents with PCOS? J Turk Ger Gynecol Assoc 2014; 15: 49-55. [CrossRef]
18. Souter I, Baltagi LM, Kuleta D, Meeker JD, Petrozza JC. Women, weight, and fertility: The effect of body mass index on the outcome of superovulation/intrauterine insemination cycles. Fertil Steril 2011; 95: 1042-7. [CrossRef]
19. Fridstrom M, Sjoblom P, Pousette A, Hillensjo T. Serum FSH levels in women with polycystic ovary syndrome during ovulation induction using down-regulation and urofollitropin. Eur J Endocrinol 1997; 136: 488-92. [CrossRef]
20. Remorgida V, Giordano M, Lanera P, Costantini S, de Cecco L. The relationship between body composition and plasma concentrations of exogenously administered urinary follicle stimulating hormone. Hum Reprod 1993; 8: 1001-4.
21. Metwally M, Cutting R, Tipton A, Skull J, Ledger WL, Li TC. Effect of increased body mass index on oocyte and embryo quality in IVF patients. Reprod Biomed Online 2007; 15: 532-8. [CrossRef]
22. Carrell DT, Jones KP, Peterson CM, Aoki V, Emery BR, Campbell BR. Body mass index is inversely related to intrafollicular HCG concentrations, embryo quality and IVF outcome. Reprod Biomed Online 2001; 3: 109-11. [CrossRef]
23. Bellver J, Ayllon Y, Ferrando M, Melo M, Goyri E, Pellicer A, et al. Female obesity impairs in vitro fertilization outcome without affecting embryo quality. Fertil Steril 2010; 93: 447-54. [CrossRef]
24. Shoham Z. The clinical therapeutic window for luteinizing hormone in controlled ovarian stimulation. Fertil Steril 2002; 77: 1170-7. [CrossRef]
25. Fanchin R, Schonauer LM, Cunha-Filho JS, Mendez Lozano DH, Frydman R. Coordination of antral follicle growth: basis for innovative concepts of controlled ovarian hyperstimulation. Semin Reprod Med 2005; 23: 354-62. [CrossRef]
26. Griesinger G, Diedrich K, Tarlatzis BC, Kolibianakis EM. GnRH-antagonists in ovarian stimulation for IVF in patients with poor response to gonadotrophins, polycystic ovary syndrome, and risk of ovarian hyperstimulation: a meta-analysis. Reprod Biomed Online 2006; 13: 628-38. [CrossRef]
27. Metwally M, Saravelos SH, Ledger WL, Li TC. Body mass index and risk of miscarriage in women with recurrent miscarriage. Fertil Steril 2010; 94: 290-5. [CrossRef]

The effect of place of residence and lifestyle on vitamin D deficiency in pregnancy: Comparison of eastern and western parts of Turkey

Esra Bahar Gür[1], Gülüzar Arzu Turan[1], Sümeyra Tatar[1], Ayşe Gökduman[2], Muammer Karadeniz[3], Gülnaz Çelik[4], Mine Genç[1], Serkan Güçlü[1]

[1]Department of Obstetrics and Gynecology, Şifa University Faculty of Medicine, İzmir, Turkey

[2]Department of Biochemistry, Şifa University Faculty of Medicine, İzmir, Turkey

[3]Department of Endocrinology, Şifa University Faculty of Medicine, İzmir, Turkey

[4]Department of Biochemistry, Şifa Hospital, Erzurum, Turkey

Abstract

Objective: The aim of this study was to determine the prevalence and the predictive factors of vitamin D deficiency in pregnancy and the compliance with "The National Vitamin D Support Program" at Turkey's easternmost and westernmost provinces.

Material and Methods: Lifestyles of women at 24-28 weeks of pregnancy were assessed using a questionnaire form, and serum 25-hydroxyvitamin D3 (25(OH)D3) levels were measured.

Results: Vitamin D deficiency (≤20 ng/mL) in pregnant women had a prevalence of 27.8% in İzmir and 76.3% in Erzurum. The compliance of "The National Vitamin D Support Program" was 8% in İzmir and 32.6% in Erzurum. Clothing style, fish consumption, seaside holiday duration, and 1200 IU/day vitamin D replacement had an effect on $25(OH)D_3$ levels in pregnant subjects in İzmir, whereas only holiday duration and 1200 IU/day vitamin D replacement affected $25(OH)D_3$ levels in Erzurum. However, when a threshold for 25(OH)D3 level was considered ≥32 ng/mL, lifestyles did not affect $25(OH)D_3$ level.

Conclusion: The effect of lifestyle on $25(OH)D_3$ level in pregnancy is limited, especially in cold regions. We recommended increasing the compliance with "The National Vitamin D Support Program" at the follow-up of all pregnant women, irrespective of region and season.

(J Turk Ger Gynecol Assoc 2014; 15: 149-55)

Key words: Pregnancy, vitamin D deficiency, vitamin D replacement, lifestyle, place of residence

Received: 15 April, 2014 **Accepted:** 09 July, 2014

Introduction

Vitamin D is a cholesterol derivative steroid hormone that, unlike other vitamins, can be synthesized in the human body. Apart from its known role in calcium metabolism, it has important additional roles in many cellular events by virtue of its autocrine and paracrine effects. It leads to anti-inflammatory and anti-infective responses and regulates cellular proliferation, differentiation, and insulin synthesis (1, 2). Recent studies have shown that vitamin D has an important role in both healthy pregnancy processes and long-term health of offspring. Recent evidence has suggested that vitamin D has an association with multifactorial diseases of pregnancy, such as bacterial vaginosis, preterm birth, gestational diabetes, and preeclampsia (3-5). In addition, some epidemiologic studies reported that there might be a relationship between allergic diseases, asthma, diabetes mellitus type 1, schizophrenia, and autism and maternal vitamin D deficiency (6-8).

The prevalence of vitamin D deficiency in pregnancy is high all over the word. Classically, conditions, such as a low socioeconomic level, being of African or Latin American descent, obesity, dark skin color, wearing covering clothing, living in northern latitudes, and taking no vitamin D supplements, are known to be associated with vitamin D deficiency. However, high vitamin D deficiency rates have recently been detected in people not usually considered to be 'at risk': with a lighter skin color, have a holiday for a long time, have a higher socioeconomic level, living from sun-drenched, torrid zones, and those believed to have adequate sun exposure (9-11).

The best indicator of vitamin D status is serum 25-hydroxyvitamin D3 ($25(OH)D_3$) concentration, because it reflects both dietary intake from vitamin D and cutaneous synthesis of vitamin D. However, there is no absolute consensus as to what a normal range for $25(OH)D_3$ in pregnancy should be. Most authors agree that severe vitamin D deficiency should be defined by a $25(OH)D_3$ concentration ≤10 ng/mL (≤25

Address for Correspondence: *Esra Bahar Gür, Department of Obstetrics and Gynecology, Şifa University Faculty of Medicine, İzmir, Turkey. Phone: +90 505 653 55 48 e.mail: esrabaharg@yahoo.com*

DOI:10.5152/jtgga.2014.13048

nmol/L) and mild vitamin D deficiency by a $25(OH)D_3$ concentration 10-20 ng/mL (25-50 nmol/L); but, recent evidence suggests that the optimal serum $25(OH)D_3$ levels may be even higher than >32 ng/mL (>80 nmol/L) (4).

Routine screening for vitamin D deficiency in pregnancy is not considered a cost-effective option. However, many health organizations recommend vitamin D supplementation during pregnancy. But, these issues, such as if vitamin D replacement will be given to all pregnant women or only to high-risk pregnant women, regional and seasonal differences, and the effective and safe dose of vitamin D in pregnancy, are still not clear, and further research is needed concerning these issues.

In the present study, we aimed to a) examine the prevalence of vitamin D deficiency in pregnancy at two extreme geographical points of Turkey; b) examine the effect of different geographical locations in the same latitudes and different lifestyles in the same ethnic origin to vitamin D deficiency prevalence; c) examine the compliance with "The National Vitamin D Support Program for Pregnancy;" and d) inform on future screening and/ or supplementation strategies.

Material and Methods

İzmir and Erzurum are very distinct provinces of Turkey with respect to both geographical and climatic conditions and social life. They are located in similar latitudes (39.55 North and 38.25 North). İzmir lies on the westernmost point of Turkey (27.0 East). It is located on the Aegean Sea coast and has an altitude of 2 m. According to the Turkish Directorate of Meteorology, the average temperature in the study period was 22.6°C daily. Uncovered clothing is common among women. Thanks to its coastal location, rates of sea and fish consumption are high. Erzurum, on the other hand, is located at the easternmost point of Turkey (41.1 East). The city lies in mountainous terrain with an altitude of 1893 m. The average temperature in the study period was 12.3°C. Among women, Islamic covered clothing style and domestic life are common. Local cuisine typically does not contain seafood.

The present study was approved by the local ethical committee at Şifa University, written consent was obtained to participate, and the procedures followed were in accordance with the Helsinki Declaration of 1975 (revised in 2008). The study data were collected from Erzurum Şifa Hospital and Şifa University, Bornova Health Research and Application Hospital, between June 2012 and October 2012.

Vitamin D status was defined by serum levels of $25(OH)D_3$ as follows: severe vitamin D deficiency, $25(OH)D_3$ ≤10 ng/mL (25 nmol/L); mild vitamin D deficiency, $25(OH)D_3$ of 10-20 ng/mL (25-50 nmol/L); normal ≥20 ng/mL (50 nmol/L), and optimal status, $25(OH)D_3$ ≥32 ng/mL (80 nmol/L).

Collection of the Study Data

Voluntary women at 24-28 weeks of pregnancy attending routine antenatal review or glucose challenge tests were the source population. Subjects with diabetes mellitus, hypertension, chronic liver and renal disease, rheumatic disease, gastrointestinal diseases with malabsorption, and other chronic diseases, as well as subjects on chronic medical therapy were excluded. In total 687 participants, 387 participants in İzmir Bornova Health Research and Application Hospital and 245 participants in Erzurum Şifa Hospital; were founded suitable for study criteria in this period. Eligible women were questioned via a questionnaire form about their lifestyle, and blood samples were taken for $25(OH)D_3$ levels.

The questionnaire form offered to the participants included questions about annual income, educational level; parity; smoking; the frequency of exposure to sunlight; clothing style; using sunscreen; seaside holiday duration within the last 6 months; status of fish, milk, egg, and vitamin D-enriched food consumption; and status of vitamin D and multivitamin use. Occupational status of the pregnant women was also assessed. The frequency of exposure to sunlight was questioned in terms of number of days of exposure in a week, not less than 30 minutes. Covered clothing style was defined as clothing covering all body parts except for the hands and face. Consumption of a half-liter milk or milk product was considered adequate. Fruit juice, margarines, and breakfast brittles are fortified with vitamin D and widely used in Turkey. However vitamin D-fortified milk is not used in our country. Regular use of at least one of these products was questioned under the title of vitamin D-enriched food consumption.

Skin color of the participants was classified according to the Fitzpatrick Skin Color Scale. Starting from 1 point up to 6, a score was given to each subject.

Body mass index (BMI, weight (kg)/height $(m)^2$) was calculated by measuring the height and body weight simultaneously with blood collection.

$25(OH)D_3$ level may be affected by lifestyles, personal characteristics, and living place. We aimed that to create study groups with similar personal characteristics in both provinces to better understand the opportunity of lifestyles to affect vitamin D deficiency. For this reason, the study groups was defined as follows: a) skin color <4 according to Fitzpatrick Skin Color Scale, b) BMI 20-30 kg/m^2, c) parity ≤3, d) educational level ≥8 year, e) annual income ≥$4500, f) Caucasian ethnicity, and f) age 18-40. Afterwards, the study groups were created according to the questionnaires of participants. As a result, 208 pregnant were included in the study. Figure 1 represents a flowchart of the study design.

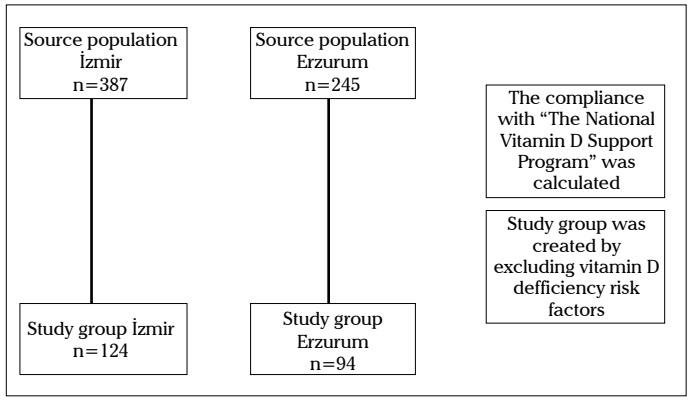

Figure 1. Flow chart of the study design

Collection of Blood Samples

Blood samples collected in Erzurum were sent to İzmir at -20°C under protection from sunlight. All laboratory analyses were performed in a single laboratory. 25(OH)D_3 level was analyzed by ELISA (EUROIMMUN, D-23560 Lübeck, Seekamp 31, Germany) method.

Statistical Analysis

Statistical analysis was performed by using the SPSS (15.0) for Windows (SPSS Inc., Chicago, IL, USA). Categorical variables were analyzed by forming a crosstable for inter-group differences, and χ^2 analysis was performed. For 25(OH)D_3 level, t-test for comparison of 2 groups was used. Variables within a group were analyzed using ANOVA test. A significant ANOVA test result was further analyzed with Bonferroni test when the variance was homogenous and Dunnett T3 test when it was not. A 2-sided analysis of variance was done for 25(OH)D_3 by considering the province and the variables. A logistic regression analysis was performed for predictor factors of vitamin D deficiency, with 2 separate analyses being performed by assuming threshold values of 20 and 32. A p value less than 0.05 was considered statistically significant.

Results

In total, 387 participants in Bornova Health Research and Application Hospital and 245 participants in Erzurum Sifa Hospital were accepted for study. Usage of vitamin D in pregnancy in İzmir and Erzurum and compliance with "The National Vitamin D Support Program for Pregnancy" were calculated. Afterwards, study groups were created according to the personal characteristics of the participants. As a result, 124 pregnant women in İzmir and 94 pregnant women in Erzurum were included in the study.

The mean age was 28.4±4.5 in the İzmir study group and 29.1±5.1 in the Erzurum study group, the mean gestational week was 25.2±3.1 in the İzmir study group and 26.1±5.4 in the Erzurum study group, and BMI averaged 27.1±3.5 in İzmir and 26.6±3.3 in Erzurum, with no significant difference between the groups.

Table 1. Vitamin D usage in İzmir and Erzurum

Regular vitamin D replacement*	1200 IU/day (n, %)	400 IU/day (n, %)	No vitamin D replacement (n, %)
İzmir (n=387)	31 (8%)	325 (83.9%)	31 (8%)
Erzurum (n=245)	80 (32.6%)	157 (64%)	8 (3.2%)
*Regular vitamin D replacement: ≥3 day/week			

Compliance with "The National Vitamin D Support Program"

We found that 8% of pregnant women in İzmir and 32.6% of pregnant women in Erzurum took 1200 IU/day vitamin D, the recommended dose of The National Program, and 83.9% of pregnant women in İzmir and 64% of pregnant women in Erzurum used 400 IU/day vitamin D (multivitamin). Furthermore, we observed that 8% of pregnant women in İzmir and 3.2% of pregnant women in Erzurum did not take vitamin D supplementation. Vitamin D usage in İzmir and Erzurum is given in Table 1.

Serum 25(OH)D_3 Levels by Provinces

25(OH)D_3 levels by provinces are given in Table 2. Severe vitamin D deficiency was present in 11.2% of the İzmir group and 17% of the Erzurum group. Mild vitamin D deficiency was present in 23.3% of the İzmir group and 58.5% of the Erzurum group. Normal vitamin D level rate (≥20 ng/mL) was 65.3% in İzmir and 24.4% in Erzurum. However, 34% of pregnant subjects from İzmir and only 1% of those from Erzurum had optimal 25(OH)D_3 levels (≥32 ng/mL). Average 25(OH)D_3 level was 38 ng/mL (±3.6 standard deviation (SD)) in İzmir and 16 ng/mL (±5.8 SD) in Erzurum.

Factors Associated with Serum 25(OH)D_3 Level

Effects of lifestyle factors on 25(OH)D_3 level were separately assessed for İzmir and Erzurum. While uncovered clothing, fish consumption, a longer seaside holiday duration, and 1200 IU/day vitamin D replacement significantly increased 25(OH)D_3 level in pregnant subjects living in İzmir, long holiday duration and 1200 IU/day vitamin D replacement affected 25(OH)D_3 in the Erzurum group. The effects of lifestyle factors on local 25(OH)D_3 levels are summarized in Table 3.

Assuming the threshold level as 20 ng/mL, logistic regression analysis showed that covered clothing style by 2.9-fold, holiday duration less than 1 week by 23.5-fold, vitamin D replacement less than 3 days a week and less than 1200 IU/day by 6.2-fold, consuming fish less than once a week by 1.6-fold, and living in Erzurum by 38.3-fold were increased the risk of vitamin D deficiency. A threshold of 32 ng/mL, on the other hand, made living in Erzurum the only effective factor that increased vitamin D deficiency risk by 33.5-fold. The results of the multivariate logistic regression analysis are summarized in Tables 4 and 5.

Discussion

Data from eastern and western parts of Turkey showed that even in summer and fall, the prevalence of vitamin D deficiency in pregnancy is high in our country, although the vitamin D defi-

Table 2. 25(OH)D_3 levels in İzmir and Erzurum

25(OH)D_3 level (ng/mL)	Severe deficiency (≤10 ng/mL)	Mild deficiency (10-20 ng/mL)	Normal level (≥20 ng/mL)	Optimal level (≥32 ng/mL)	Average level (±SD)	p value
İzmir (n, %)	14 (11.2)	29 (23.3)	81 (65.3)	38 (34)	38 (3.6)	<0.001
Erzurum (n, %)	16 (17)	55 (58.5)	23 (24.4)	1 (1)	16 (5.8)	
SD: standard deviation. 25(OH)D_3: 25-hydroxyvitamin D3						

Table 3. Associations between lifestyle and 25(OH)D_3 level

Predictor factors 25(OH)D_3 level	25(OH)D_3 level İzmir (ng/mL)	p value	25(OH)D_3 level Erzurum (ng/mL)	p value
State of employment				
Employed	22	0.08	15.8	0.9
Unemployed	26.5		16.2	
Clothing style		0.03		0.4
Covered clothing	24.5		15	
Uncovered clothing	31.6		17.9	
Smoking		0.9		0.7
Smokers	29.2		18.4	
Non-smokers	28.1		17.3	
Seaside holiday duration				
<1 week/last 6 month	15.4	<0.01	13.8	<0.01
≥1 week/last 6 month	31.8		20.8	
Sun exposure		0.5		0.9
≥3 day/week	27.1		16.5	
<3 day/week	28.2		15	
Using sunscreen		0.2		0.6
Sometimes	30		18.4	
Never	26.9		15.5	
Fish consumption		0.04		0.1
≥1 day/week	30.3		17.9	
More rare	23.2		15.8	
Egg consumption		0.5		0.4
≥3 day/week	27.1		15.7	
<3 day/week	27.5		16	
Vitamin D-enriched food consumption		0.6		0.1
≥3 day/week	27.2		14.8	
<3 day/week	29.3		14.6	
Milk consumption		0.4		0.5
≥3 day/week	29.4		15.8	
<3 day/week	25.3		17.1	
1200 IU/day Vitamin D supplement		0.04		0.03
≥3 day/week	35.7		21.9	
<3 day/week	27.7		14.1	
400 IU/day Vitamin D supplement		0.07		0.7
≥3 day/week	29.7		16.9	
<3 day/week	24.1		13.7	

Statistical evaluation was made with ANOVA. P<0.05 statistical significance.
25(OH)D_3: 25-hydroxyvitamin D3

ciency prevalence was significantly lower in İzmir (76.3% versus 27.8%). It would not be surprising to see much lower levels in winter. Hence, a study by Halicioglu et al. (12) that examined winter and spring levels of 25(OH)D_3 in 256 pregnant women living in İzmir reported a vitamin D deficiency (≤20 mg/mL) prevalence of 90.3% and a normal level (≥30 mg/mL) in only 0.4%. Other studies from Turkey have reported that pregnancy-associated vitamin D deficiency remains a commonly seen problem (13-17). However, to our knowledge, the present study is the only study that has compared the difference in vitamin D

Table 4. Significant predictive factors for vitamin D deficiency

Significant predictive factors for vitamin D deficiency (threshold ≥20 ng/mL)	Odds ratio	95% CI	p value
Living place *(Living in İzmir versus living in Erzurum)*	38.3	1.1-1276	0.04
Clothing style *(uncovered versus covered clothing)*	2.9	1.1-7.9	<0.02
Seaside holiday duration *(≥1 week/ last 6 month/ versus <1 week/last 6 month)*	23.5	7.0-78.1	<0.001
1200 IU/day Vitamin D *supplement (≥3 day/week versus consuming less than)*	6.2	1.2-4.1	<0.02
Fish consumption *(≥1 day/week versus consuming less than)*	1.6	1.6-4.1	<0.03
Multivariate logistic regression was made. The threshold was considered ≥ 20 ng/mL			

Table 5. Significant predictive factors for vitamin D deficiency

Significant predictive factors for vitamin D deficiency (the threshold ≥32 ng/mL)	Odds ratio	95% CI	p value
Living place *(Living in İzmir versus living in Erzurum)*	33.5	3.8-296	0.02
Multivariate logistic regression was made. The threshold was considered ≥32 ng/mL			

deficiency prevalence in pregnancy between regions of Turkey. Behavioral factors and personal characteristics can affect $25(OH)D_3$ level (9). We aimed to create study groups with similar personal characteristics in both provinces to better understand the lifestyle effects on vitamin D deficiency. In our study, we observed that clothing style, seaside holiday duration, consuming fish, and 1200 IU/day vitamin D supplement affected $25(OH)D_3$ level.

The body surface area required for ideal $25(OH)D_3$ synthesis is not entirely known. In a study by Perampalam et al. (9), it was found that the critical body surface area required for sustaining an adequate $25(OH)D_3$ level was >27% and that the body surface area exposed to sunlight was the main behavioral factor related to $25(OH)D_3$ level. In Islamic clothing (hands and face uncovered), 8% of the total body surface area remains uncovered.

Among the dietary sources, the only ones that seem to affect $25(OH)D_3$ synthesis are fish. However, 56% of the pregnant women in İzmir and 82% of those residing in Erzurum consumed fish less than once a week. Seafood is also a good source of omega-3 fatty acids, and it contains high-quality proteins (18). Promoting fish consumption in pregnant women may be reasonable with respect to $25(OH)D_3$ levels. In our study, we did not detect a relationship between vitamin D-enriched foods and $25(OH)D_3$ levels. This situation can be explained by the limited vitamin D-reinforced food in Turkey (15), whereas in a study by Charatcharoenwitthaya et al. (19), it was found that drinking vitamin-fortified milk affected $25(OH)D_3$ levels in pregnancy.

Surprisingly, although we found that seaside holiday duration affected $25(OH)D_3$ level in both İzmir and Erzurum, we did not detect any relationship between sunlight exposure duration and $25(OH)D_3$ levels. This situation can be explained by factors, such as exposure to sunlight at times other than noon, covering clothing style, and use of sunscreen. Using sunscreen prevents vitamin D synthesis, disallowing ultraviolet B (UVB) rays to penetrate the skin. Our study may not have had the ability to detect effects of using sunscreen on vitamin D levels, since the rates of sunscreen use were as low as 11% and 20% in the groups. Additionally, since UVB rays have a short wavelength, $25(OH)D_3$ synthesis reaches the top at noon, when the sunlight hits the earth at a perpendicular angle. Even 30 minutes of sunbathing without using sunscreen at noon may lead to synthesis of $25(OH)D_3$ at an amount of 15-20,000 IU (20, 21). Therefore, having adequate sun exposure may not mean having adequate $25(OH)D_3$ levels.

In our study, we found that a vitamin D dose of 400 IU/day in multivitamins did not affect $25(OH)D_3$ level. On the other hand, $25(OH)D_3$ levels increased in women using a dose of 1200 IU/day. There is no consensus with regard to vitamin D replacement to sustain a normal $25(OH)D_3$ level for healthy pregnancy. The National Health Institute recommends 400 IU/day, and the World Health Organization recommends 200 IU/day vitamin D supplementation for pregnant women (22). Recent studies have shown that the official vitamin D dosing recommendations are far from meeting the demands of pregnancy, and $25(OH)D_3$ levels may be more effectively boosted with doses as high as 1600, 2000, and 4000 IU/day, without increasing side effects (23, 24). Wagner et al. (25) reported that serum $25(OH)D_3$ levels did not change significantly until after vitamin D supplementation exceeded 1000 IU/day. The dose that leads to vitamin D intoxication is not precisely known; however, vitamin D intoxication can be considered an extremely rare and exaggerated condition. The National Health Institution has reported that 4000 IU/day is the upper safe limit for pregnant women (22). No side effects have been reported in volunteer non-pregnant women at doses of 10,000 IU/day (26). It seems that the recommended supplementation doses will increase as the number of randomized controlled studies on this subject increases.

In Turkey, until May 2011, a health policy on vitamin D prophylaxis for pregnant women did not exist; thus, the vitamin D supplements prescribed for pregnant women were limited to low doses (200-400 IU), amounts generally included in commercial multivitamin preparations. Since 2011, the Turkish Ministry of Health has recommended vitamin D supplementation to all pregnant women at a dose of 1200 IU/day starting from 12 weeks of pregnancy (27). However, 8% of the İzmir group and 32.6% of the Erzurum group were taking vitamin D at recommended doses in our study groups. Our study found that the

compliance "The National Vitamin D Support Program" is poor. In our study, we found that the threshold was 32 ng/mL instead of 20 ng/mL for normal levels of $25(OH)D_3$, the living place was the only effective factor for vitamin D deficiency, and lifestyle did not affect $25(OH)D_3$ level. Furthermore, only one-third of pregnant women living İzmir had optimal $25(OH)D_3$ levels, even in summer and fall. For this reason, it seems reasonable to taking all pregnant subjects irrespective of region and season "The National Vitamin D Support Program." In our study, the average $25(OH)D_3$ level of pregnant women who took 1200 IU/day vitamin D in Erzurum was 21.9 ng/mL. It is suggested that a dose of 1200 IU/day vitamin D during the winter months in Erzurum may not be sufficient. The dose of vitamin D may have to be increased, or pregnant women living in cold regions may be screened for vitamin D levels.

There are some limitations of our study. One of them is that the study could not reflect seasonal differences, because the study was only conducted in the summer and fall, and the other is that we created study groups with similar personal characteristics in both provinces to better understand the lifestyle effects on vitamin D deficiency. Consequently, the study groups were small.

In conclusion, prevalence of vitamin D deficiency in pregnancy is high in Turkey even, in the sunny season. Behavioral factors are more effective on $25(OH)D_3$ levels in pregnancy in sun-drenched regions. Living in high-altitude cold regions seems to be the most powerful risk factor for vitamin D deficiency. Even in sun-drenched regions, only one-third of pregnant subjects had ideal $25(OH)D_3$ levels. Vitamin D supplementation is a cheap, safe, and effective means to fight vitamin D deficiency. It is recommended to increase compliance with "The National Vitamin D Support Program" at follow-up of all pregnant women, irrespective of region and season. The reasons of poor compliance with this program should be investigated. For more precise recommendations, more randomized, controlled studies on vitamin D deficiency in pregnancy are needed.

Ethics Committee Approval: *Ethics committee approval was received for this study from the ethics committee of Şifa University.*

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

Peer-review: *Externally peer-reviewed.*

Author contributions: *Concept - E.B.G., S.G.; Design - E.B.G., S.G.; Supervision - M.K., S.G.; Resource - E.B.G., G.A.T., S.T.; Materials - S.T., A.G., G.C.; Data Collection&/or Processing - E.B.G., A.G., G.C.; Analysis&/or Interpretation - M.G.; Literature Search - M.G.; Writing - E.B.G., S.G.; Critical Reviews - M.K., S.G.*

Acknowledgements: *We are grateful for the assistance during the study period to hospital management of Erzurum Şifa Hospital.*

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

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

References

1. Norman AW. From vitamin D to hormone D: Fundamentals of the vitamin D endocrine system essential for good health. Am J Clin Nutr 2008; 88: 491-9.
2. Bikle D. Nonclassic actions of vitamin D. J Clin Endocrinol Metab 2009; 94: 26-34. [CrossRef]
3. Kovacs C. Vitamin D in pregnancy and lactation: Maternal, fetal, and neonatal outcomes from human and animal studies. Am J Clin Nutr 2008; 88: 520-8.
4. Hollis BW, Wagner CL. Assessment of dietary vitamin D requirements during pregnancy and lactation. Am J Clin Nutr 2004; 79: 717-26.
5. Holick MF, Chen TC. Vitamin D deficiency: A worldwide problem with health consequences. Am J Clin Nutr 2008; 87: 1080-6.
6. Litonjua AA, Weiss ST. Is vitamin D deficiency to blame for the asthma epidemic? J Allergy Clin Immunol 2007; 120: 1031-5. [CrossRef]
7. Stene LC, Ulriksen J, Magnus P, Joner G. Use of cod liver oil during pregnancy associated with lower risk of Type I diabetes in the offspring. Diabetologia 2000; 43: 1093-8. [CrossRef]
8. McGrath JJ, Welham JL. Season of birth and schizophrenia: A systematic review and metaanalysis of data from the Southern Hemisphere. Schizophr Res 1999; 35: 237-42.[CrossRef]
9. Perampalam S, Ganda K, Chow KA, Opıe N, Hıckman PE, Shadbolt B, et al. Vitamin D status and its predictive factors in pregnancy in 2 Australian populations. Aust N Z J Obstet Gynaecol 2011; 51: 353-9. [CrossRef]
10. Feleke Y, Abdulkadir J, Mshana R, Mekbib TA, Brunvand L,Berg JP. Low levels of serum calcidiol in an African population compared to a North European population. Eur J Endocrinol 1999; 141: 358-60. [CrossRef]
11. Farrant HJ, Krishnaveni GV, Hill JC, Boucher BJ, Fisher DJ, Noonan K. Vitamin D insufficiency is common in Indian mothers but is not associated with gestational diabetes or variation in newborn size. Eur J Clin Nutr 2009; 63: 646-52. [CrossRef]
12. Halicioglu O, Aksit S, Koc F, Akman SA, Albudak E, Yaprak I, et al. Vitamin D deficiency in pregnant women and their neonates in spring time in western Turkey. Paediatr Perinat Epidemiol 2012; 26: 53-60. [CrossRef]
13. Ustuner I, Keskin HL, Tas EE, Neselioglu S, Sengul O, Avsar AF. Maternal serum 25(OH)D levels in the third trimester of pregnancy during the winter season. J Matern Fetal Neonatal Med 2011; 24: 1421-6. [CrossRef]
14. Hatun S, Islam O, Cizmecioglu F, Kara B, Babaoglu K, Berk F. Subclinical vitamin D deficiency is increased in adolescent girls who wear concealing clothing. J Nutr 2005; 135: 218-22.
15. Alagöl F, Shihadeh Y, Boztepe H, Tanakol R, Yarman S, Azizlerli H, Sandalci O. Sunlight exposure and vitamin D deficiency in Turkish women. J Endocrinol Invest 2000; 23: 173-7. [CrossRef]
16. Pehlivan I, Hatun S, Aydoğan M, Babaoğlu K, Gökalp AS. Maternal vitamin D deficiency and vitamin D supplementation in healthy infants. Turk J Pediatr 2003; 45: 315-20.
17. Ergür AT, Berberoğlu M, Atasay B, Şıklar Z, Bilir P, Arsan S, et al. Vitamin D deficiency in Turkish mothers and their neonates and in women of reproductive age. J Clin Res Pediatr Endocrinol 2009; 1: 266-9. [CrossRef]
18. Canda MT, Sezer O, Demir N. An audit of seafood consumption awareness during pregnancy and its association with maternal and fetal outcomes in a Turkish population. J Obstet Gynecol 2011; 31: 293-7. [CrossRef]

19. Charatcharoenwitthaya N, Nanthakomon T, Somprasit C, Chanthasenanont A, Chailurkit LO, Pattaraarchachai J, Ongphiphadhanakul B. Maternal vitamin D status, its associated factors and the course of pregnancy in Thai women. Clin Endocrinol (Oxf) 2013; 78: 126-33. [CrossRef]
20. Krause R, Buhring M, Hopfenmuller W. Ultraviolet B and blood pressure. Lancet 1998; 352: 709-10. [CrossRef]
21. Holick MF. Environmental factors that influence the cutaneous production of vitamin D. Am J Clin Nutr 1995; 61: 638-45.
22. Doets EL, de Wit LS, Dhonukshe-Rutten RA, Cavelaars AE, Raats MM, et al. Current micronutrient recommendations in Europe: Towards understanding their differences and similarities. Eur J Nutr 2008; 47: 17-40. [CrossRef]
23. Wagner CL, McNeil R, Hamilton SA, Winkler J, Rodriguez Cook C, Warner G, et al. A randomized trial of vitamin D supplementation in 2 community health center networks in South Carolina. Am J Obstet Gynecol 2013; 208: 137.e1-13.
24. Hollis BW, Wagner CL. Nutritional vitamin D status during pregnancy: Reasons for concern. CMAJ 2006; 174: 1287-90. [CrossRef]
25. Wagner CL, Hulsey TC, Fanning D, Ebeling M, HollisBW. High-dose vitaminD3 upplementation in a cohort of breastfeeding mother sand thei infants: a 6-month follow-up pilot study. Breastfeed Med 2006; 1: 59-70. [CrossRef]
26. Vieth, R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. Am J Clin Nutr 1999; 69: 842-56.
27. Gur G, Abacı A, Koksoy AY, Anık A, Catlı G, Kıslal FM, et al. Incidence of maternal Vitamin D deficiency in a region of Ankara, Turkey: a preliminary study. Turk J Med Sci 2014; 44: doi:10.3906/sag-1304-107. [CrossRef]

Reproducibility of a time-lapse embryo selection model based on morphokinetic data in a sequential culture media setting

Ender Yalçınkaya, Elif G. Ergin, Eray Çalışkan, Zeynep Öztel, Alev Özay, Hakan Özörnek
Eurofertil IVF Center, İstanbul, Turkey

Abstract

Objective: To compare the outcomes of embryos that were given a dynamic score based on a preconstructed embryo scoring model and to analyze whether this model complies with our data.

Material and Methods: A total of 910 transferred embryos with known implantation data were retrospectively analyzed in this study. All of the embryos were given a dynamic score based on the preconstructed hierarchical embryo scoring model.

Results: The highest pregnancy rate was seen in groups C+ and A- (48.2% for each), and the lowest was observed in Group E (19.7%). When implantation and clinical pregnancy rates were compared between groups, it was found that the highest and statistically significant implantation and clinical pregnancy rates were seen in group C+ (32.7% for each, p=0.000). They were dropped down to 29.4% in Group A-.

Conclusion: The outcomes of the embryos based on the dynamic score do not comply with the results of the preconstructed model. Each IVF laboratory is unique based on its practice. Therefore, we suggest that each IVF laboratory should determine its own embryo selection criteria based on its own data instead of using a preconstructed model. (J Turk Ger Gynecol Assoc 2014; 15: 156-60)

Key words: Preconstructed model, dynamic score, pregnancy rate

Received: 08 May, 2014 **Accepted:** 14 July, 2014

Introduction

The limitations in the number of embryos to be transferred by the new regulations have revealed the necessity of transferring the embryo with the highest implantation potential in order to increase pregnancy rate. There are many ongoing studies that aim to determine new noninvasive criteria to select the embryo with the highest implantation potential and thus to increase overall pregnancy rates (1-4).

The most important determinants of embryo quality are the morphological parameters of the developing embryos. During conventional assisted reproduction procedures, embryos are taken out of the incubators at limited time intervals in order to protect them against the negative effects of outside environmental conditions (temperature change, pH change, etc.) (5). Therefore, there are still some question marks in mind about embryo selection, since it is impossible to obtain detailed information about the developmental process of the embryos.

Time-lapse applications in assisted reproduction are based on the determination of embryo morphokinetics through monitoring by camera systems that are located in standard incubators for embryo culture. Improvements in these applications have led to the development of devices with time lapse monitoring as well as incubation properties. Recent studies related to time lapse incubation have reported interesting development patterns and promising results (6-8). Up to date, Meseguer et al. (7) have constructed a hierarchical model that helps choose the best embryo for transfer according to their experiences.

The purpose of this study is to compare the outcomes of the embryos with known implantation data based on their dynamic scores and to analyze whether a preconstructed embryo scoring model based on morphokinetic data can comply with our data.

Material and Methods

A total of 910 transferred embryos with known implantation data were retrospectively analyzed in this study. Ethics approval was obtained for the use of all relevant data. Characteristics of the embryos are given in Table 1. All patients underwent an antagonist protocol. In the fresh stimulation cycle of an antagonist regimen, gonadotropin administration was started on day 2-3 of the menstrual cycle. Follicular development was monitored by transvaginal ultrasound at least every 2 days after 5 days of gonadotropin administration. Gonadotropin-releasing hormone (GnRH) antagonist (Cetrotide 0.25 mg; Merck Serono, Bari, Italy) was started on stimulation day 6, when the leading follicle reached a diameter of 13-14 mm, and was used every day until human chorionic gonadotropin (hCG) administration. Finally, a single injection of

Address for Correspondence: *Ender Yalçınkaya, Eurofertil IVF Center, İstanbul, Turkey.*
Phone: +90 507 191 04 32 e.mail: endersu81@gmail.com

DOI:10.5152/jtgga.2014.13068

Table 1. Demographic data of the embryos. The data are presented as numbers (percentages) or mean±standard deviation (SD) from the mean

Variable	Dynamic score (based on Meseguer's model)									p value
	A+	A-	B+	B-	C+	C-	D+	D-	E	
Age (years)	31±5.1	30±4.7	31.2±5.8	31.8±5.3	30.4±5.4	31.4±5.9	30.7±6.1	32.2±5.6	32.5±5.2	0.08
BMI (kg/m^2)	25.3±4.0	25±4.5	24.8±3.3	24.5±3.7	25±4.3	25.2±4.0	24.8±3.3	24.7±4.2	25.4±4.9	0.95
Cause of infertility anovulation	14 (6.6)	6 (7.1)	5 (6.1)	2 (5.9)	24 (9.6)	4 (6.5)	11 (11.8)	1 (3.2)	6 (9.8)	0.09
Oligoasthenoteratospermia	66 (31.3)	37 (43.5)	31 (37.8)	14 (41.2)	75 (29.9)	21 (33.9)	37 (39.8)	14 (45.2)	26 (42.6)	
Azoospermia	11 (5.2)	4 (4.7)	6 (7.3)	1 (2.9)	18 (7.2)	3 (4.8)	10 (10.8)	2 (6.5)	4 (6.6)	
Tubal factor	33 (15.6)	3 (3.5)	10 (12.2)	1 (2.9)	24 (9.6)	10 (16.1)	14 (15.1)	1 (3.2)	8 (13.1)	
Unexplained infertility	17 (41.2)	35 (41.2)	30 (36.6)	16 (47.1)	110 (43.8)	24 (38.7)	21 (22.6)	13 (41.9)	17 (27.9)	

*p<0.05 is statistically significant
BMI: body mass index

hCG (Ovitrelle; Merck Serono, Bari, Italy) was administered to induce final follicular maturation as soon as three follicles of ≥17 mm were observed. The luteal phase was supported by micronized vaginal progesterone (Progynex ampule 200 mg; Farmako, İstanbul, Turkey), progesterone in oil (Progynex ampule 50 mg; Farmako, İstanbul, Turkey), or vaginal gel (Crinone 8% gel; Merck Serono, Bari, Italy). Progesterone supplementation was provided until the detection of clinical pregnancy or the 10th week of pregnancy at the discretion of the doctor in charge. In several cases, estrogen patch (Climara flaster 3.9; Schering, Germany) was started on the day of embryo transfer and continued until clinical pregnancy.

After controlled ovarian hyperstimulation, transvaginal ultrasound-guided oocyte retrieval was performed 36 hours after hCG injection. When follicle aspiration was finished, all oocytes were kept in culture for 2-4 hours under the conditions of 37°C, 6% CO_2, and 7% O_2 until denudation in the standard incubator. For all steps related to the embryo culture, two sequential culture media (Vitrolife; Göteborg, Sweden; and Medicult; Måløv, Denmark) were used. The oocytes were mechanically denuded 2-4 hours after oocyte pickup. Intracytoplasmic sperm injection (ICSI) procedure was performed for all metaphase II (MII) oocytes, and injected oocytes were placed into pre-equilibrated culture media. The fertilization check was performed at 16-18 hours after microinjection. Presence of two pronuclei was considered normal fertilization.

All fertilized oocytes were transferred into the wells of special dishes (EmbryoSlide; Unisense FertiliTech, Aarhus, Denmark) and placed into a time lapse incubator (EmbryoScope; Unisense FertiliTech, Aarhus, Denmark) until transfer under the conditions of 6.0% CO_2, 7.0% O_2, and 37.0°C. Day 2 transfers were excluded from the study. Only day 3 and day 5 transfers were included. All embryo transfers were performed between October 2012 and December 2013 at the Eurofertil IVF Center, Istanbul, Turkey. Dynamic scores of the embryos were determined based on a preconstructed hierarchical embryo scoring model by Meseguer et al. (7). The morphology of two day 3 transfer embryos of different dynamic scores is shown in Figure 1.

Table 2. Dynamic score classification of Meseguer et al. (7) based on cleavage timings

Category	Criteria (timings)
A+ (*)	t5 (within 48.8-56.6 h); s2≤0.76 h; cc2≤11.9 h
A-	t5 (within 48.8-56.6 h); s2≤0.76 h; cc2>11.9 h
B+	t5 (within 48.8-56.6 h); s2>0.76 h; cc2≤11.9 h
B-	t5 (within 48.8-56.6 h); s2>0.76 h; cc2>11.9 h
C+	t5 (outside 48.8-56.6 h); s2≤0.76 h; cc2≤11.9 h
C-	t5 (outside 48.8-56.6 h); s2≤ 0.76 h; cc2>11.9 h
D+	t5 (outside 48.8-56.6 h); s2>0.76 h; cc2≤11.9 h
D-	t5 (outside 48.8-56.6 h); s2>0.76 h; cc2>11.9 h
E	Uneven blastomere size at 2-cell stage Abrupt division from 1 to 3 or more cells Multinucleation at 4-cell stage

*Meseguer et al. (7) selected transfer embryos based on their morphological grading, and they found that Group A+ had the highest implantation potential

Statistical Analysis

The statistical analysis of the data was performed by using Statistical Package for Social Sciences 16.0 (SPSS Inc, Chicago, IL, USA). The continuous variables were analyzed for normality distribution with Kolmogorov-Smirnoff test. All continuous variables analyzed were normally distributed and were compared between the groups by using the analysis of variance test (ANOVA). The categorical data were compared between the two groups by using chi-square test. For all comparisons, probability p<0.05 was considered to be statistically significant.

Results

The dynamic score classification by Meseguer et al. (7) is given in Table 1. Demographic data regarding the embryos are presented in Table 2. While mean age and body mass index (BMI) were similar between groups, there was a statistically significant difference in terms of total follicle-stimulating hormone (FSH)

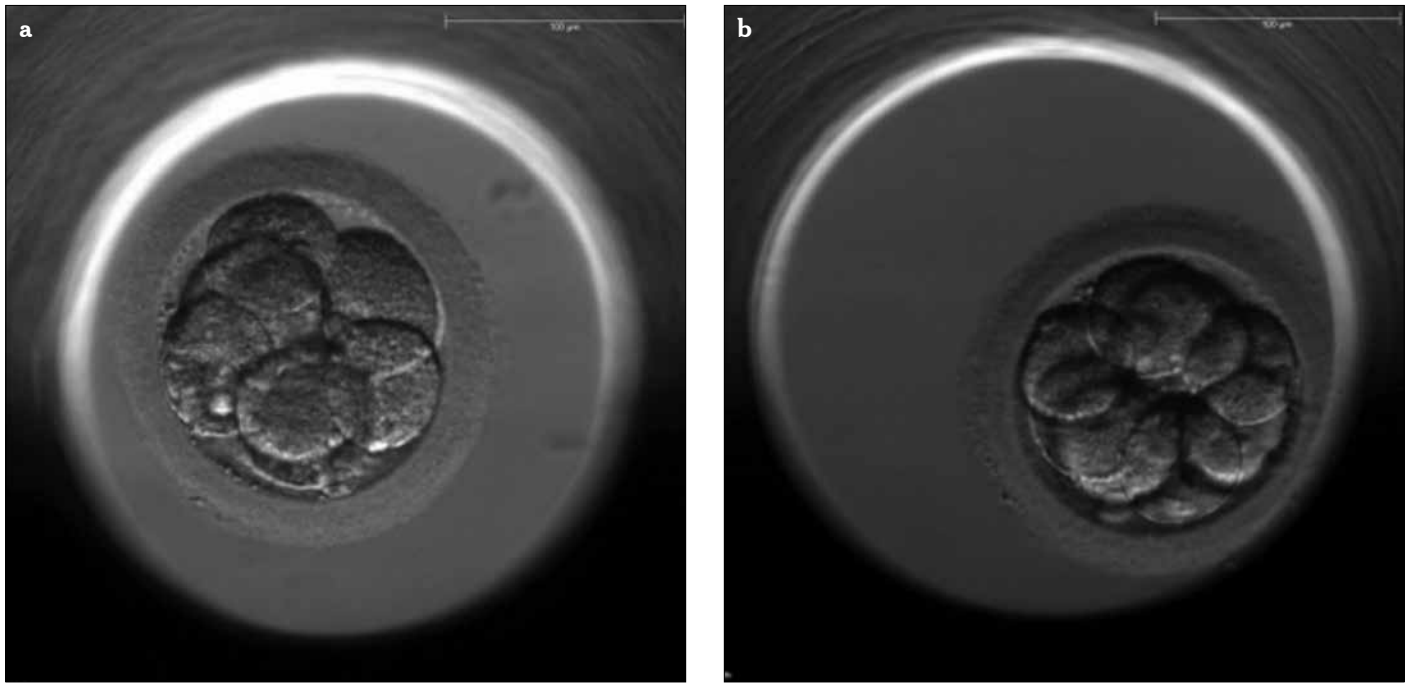

Figure 1. a, b. Figures above are two examples of transfer embryos at day 3. The photographs were captured by the camera system in time-lapse system. Embryo morphology looks similar; but dynamic scores based on embryo morphokinetics are different. Embryo with a dynamic score of A+ (a), Embryo with a dynamic score of C+ based on Meseguer's scoring model (b)

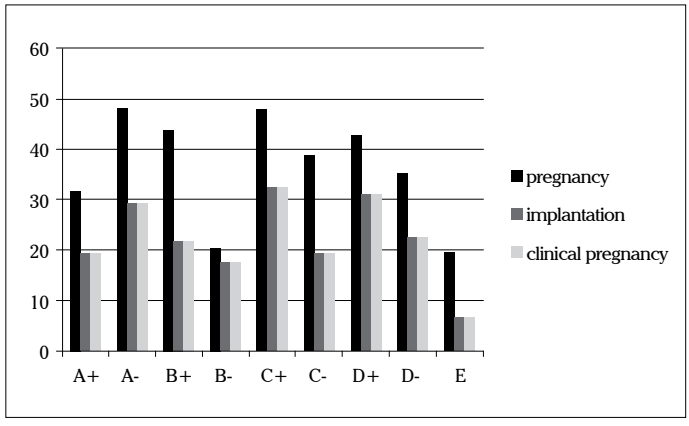

Figure 2. Comparison of the clinical outcomes of the embryos with different dynamic scores (p<0.05)

dose and number of oocytes between all groups (p=0.002 and p=0.003, respectively). When group E was excluded from the study, it was observed that there was no statistically significant difference between groups in terms of mean age, BMI, total FSH dose, and number of oocytes collected (p>0.05).

Cycle characteristics and clinical outcomes are given in Table 3, and clinical outcomes are also shown in Figure 2. The highest pregnancy rates were seen in groups C+ and A- (48.2% for each), and the lowest was observed in Group E (19.7%). When implantation and clinical pregnancy rates were compared, it was found that the highest and statistically significant implantation and clinical pregnancy rates were seen in group C+ (32.7% for each, p=0.000). They were dropped down to 29.4% in Group A-. The lowest rates were again seen in Group E (6.6% per each).

When parameters, such as the type of gonadotropin used and cause of infertility, were compared based on clinical pregnancy within each group, it was observed that there were no statistically significant differences between different types of gonadotropins and causes of infertility in terms of clinical pregnancy (p>0.05 for each). In addition, no statistically significant difference was found between groups in terms of embryo culture media and luteal support used (p>0.05).

When Group E was excluded from the analysis, it was again found that C+ had significantly higher pregnancy and implantation rates compared to other groups (p=0.003 and p=0.026, respectively). When BMI, total FSH dose, number of oocytes aspirated, and age were compared between groups except group E, no significant differences were observed (p=0.946, p=0.140, p=0.270, and p=0.314, respectively).

Discussion

Time-lapse microscopy has become a powerful technology for the study of early embryonic development in recent years. This is apparent by the publication of an increasing number of studies on this subject. Using this technique, a variety of morphological and dynamic parameters can be extracted from individual embryos and potentially used as predictive markers for healthy embryo development and used to investigate many unknown developmental questions (9). These predictive markers have gained more importance, especially in countries where single-embryo transfer is implemented, and thus, it is crucial to select the best embryo for transfer. These systems have revealed that even embryos with the same morphology on day 3 might have shown different cleavage patterns during development.

Table 3. Cycle characteristics and clinical outcomes

Variable	Dynamic score (based on Meseguer's model)									p value
	A+	A-	B+	B-	C+	C-	D+	D-	E	
Total FSH dose (IU)	2598±1009	2394±1009	2557±1639	2515±1041	2416±966	2779±1124	2507±919	2853±1224	3105±1626	0.002*
Number of oocytes aspirated	12.7±6.5	12.5±7.0	12.2±6.6	10.3±5.4	12.4±6.4	12.3±7.0	11.6±6.5	10±5.8	9±5.8	0.003*
Culture media used										
Vitrolife	109 (51.7)	51 (60)	46 (56.1)	21 (61.8)	117 (46.6)	33 (53.2)	44 (47.3)	20 (64.5)	37 (60.6)	0.12
Medicult	102 (48.3)	34 (40)	36 (43.9)	13 (38.2)	134 (53.4)	29 (46.8)	49 (52.7)	11 (35.5)	24 (39.4)	
Luteal support										
Prog.*	97 (46)	48 (56.5)	36 (43.9)	10 (29.4)	138 (55)	41 (66.1)	52 (62.7)	17 (54.8)	24 (39.3)	0.34
Prog+E2**	114 (54)	37 (43.5)	46 (56.1)	24 (70.6)	113 (45)	21 (33.9)	31 (37.3)	14 (45.2)	37 (60.7)	
Clinical outcomes										
Positive bhcg (%)	31.8	48.2	43.9	20.6	48.2	38.7	43	35.5	19.7	0.00*
Implantation rate (%)	19.4	29.4	22	17.6	32.7	19.4	31.2	22.6	6.6	0.00*
Clinical pregnancy rate (%)	19.4	29.4	22	17.6	32.7	19.4	31.2	22.6	6.6	0.00*

The data are presented as numbers (percentages) or mean±SD from the mean
*Prog: progesterone ** E2: estradiol

An incubation system with a time-lapse microscopy setting has two parts that may offer different advantages. The first part is a microscopy system that acquires continuous monitoring of the embryos, and the other is an incubation system that remains stable during data acquisition.

Time-lapse microscopy seems to offer many advantages over traditional time-point microscopy. While traditional time-point microscopy provides images at distinct time points, a time-lapse system generates continuous imaging until embryo transfer. Besides, it is connected to imaging software, and it analyzes the images by different observers, therefore decreasing inter- and intraobserver variability, since it offers repeatability of the saved images (4, 7). But, again, some variations were also seen in some time-lapse annotations in a study by Sundvall et al. (10).

The second part is the incubation stability. In a large-scale retrospective analysis by Meseguer et al. (7) comparing clinical pregnancy rates with time-lapse and standard incubation (SI), it was found that there was a significantly increased clinical pregnancy rate over those using SI. In this study, they declared the advantages of time-lapse incubation as less handling of embryos and no need for intermediate observations, which would reduce the risk of loss or contamination within the laboratory (11).

The main goal of using a time-lapse system is to be able to create a mathematical model of a scoring system from all data obtained from the embryos. For this reason, it is crucial to analyze all embryos in detail and keep the records of the clinical outcomes of each embryo. The purpose of this model is to be able to select the embryo with the highest implantation potential as early as possible. It was shown by many authors that blastocyst-stage embryo transfer was shown to increase the chance of pregnancy compared to day 3 embryo transfers (12, 13). Additional data suggest that prolonged *in vitro* culture may lead to imprinting errors and subsequent epigenetic disorders (14, 15). Because of these possible risks of extended embryo culture, a time-lapse monitoring system seems to offer the construction of an embryo scoring system that may lead the laboratory to select the embryo for transfer at an early developmental stage.

Many authors have reported different prognostic factors for better embryonic growth, and all of these parameters have focused mostly on developmental processes before day 3, and they suggested that the quality of the embryo was predetermined before embryonic gene activation (4, 7, 8). Meseguer et al. (7) constructed the first embryo scoring model that gives a dynamic score, varying between A+ to F, to each embryo based on the correlation between several developmental timings and the clinical pregnancy outcomes they present. According to their model, embryos with a dynamic score of A+ had the highest implantation potential compared to the others. In our study, we used Meseguer's model to classify our embryos that were transferred, and our results showed that C+ plus embryos had the highest implantation potential compared to the others, showing that the model constructed by Meseguer et al. (7) does not comply with our data. There may be some possible reasons for that difference, depending on the laboratory conditions and techniques used.

First of all, Meseguer et al. (7) used single-step culture media, and we used sequential culture media for embryo culture. In the study by Basile et al. (16) comparing two types of culture media, they did not find any significant differences between them. Ciray et al. (17) also compared two different types of culture media in their study and found that the embryos that were

cultured in single-step media reached the 2- to 5-cell stages earlier compared to the ones in sequential media. However, clinical pregnancy rates were similar between groups. Although it does not change overall outcome, it may cause a change in the scoring model, since it has the possibility of changing embryo kinetics. This may be a possible reason why our results based on the dynamic scores of Meseguer's model did not give the same morphokinetic outcomes.

Secondly, they were not using an O_2-controlled time-lapse incubation system. There are several studies evaluating the effect of oxygen on embryonic development and kinetics in the literature. Based on the results of these studies, it is now known that high oxygen levels during culture have a negative effect on embryonic development. Kirkeegaard et al. (18) evaluated the effect of oxygen concentration on embryos and evaluated their development by time-lapse monitoring. According to the results of their study, it was found that the timing of the third cleavage cycle (division to 8 cells) for embryos that were cultured under high oxygen concentrations was delayed. Wale and Gardner performed a similar study in mouse embryos and observed that oxygen can influence mouse embryo development at both the cleavage stage and post-compaction stages (19). In our study, we used 7% O2 for the embryo culture, and it is possible that this level could have affected the kinetics of our embryos in a different pattern compared to Meseguer's model.

In our study, the lowest clinical pregnancy rate was observed in group E, complying with Meseguer's model. This is an expected outcome, since group E was composed of embryos that had not shown a proper cleavage pattern. There were significant differences between all groups in terms of total FSH dose and number of oocytes aspirated. In order to see if group E created this difference, we made another analysis by excluding group E. Based on this analysis, it was found that both parameters did not show any statistical difference between other groups, suggesting that group E creates this confounding effect and includes the embryos of patients who were poor responders or advanced in age who needed more FSH doses.

Our results showed that variations in different laboratories may result in different embryo developmental criteria. Thus, we suggest that each IVF laboratory should determine its own embryo selection criteria based on its own data instead of using a preconstructed model.

Ethics Committee Approval: *Ethics committee approval was received for this study.*

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

Peer-review: *Externally peer-reviewed.*

Author contributions: *Concept - E.Ç., E.G.E., E.Y.; Design - E.Ç., E.G.E, E.Y.; Supervision - H.Ö., A.Ö.; Resource - Z.Ö., E.Y., E.G.E. ; Materials - E.Y., Z.Ö.; Data Collection&/or Processing - Z.Ö., E.Y.; Analysis&/or Interpretation - E.Ç., E.Y.; Literature Search - E.G.E., E.Y.; Writing - E.Y.; Critical Reviews - A.Ö., H.Ö.*

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

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

References

1. Seli E, Sakkas D, Scott R, Kwok SC, Rosendahl SM, Burns DH. Noninvasive metabolomic profiling of embryo culture media using Raman and near-infrared spectroscopy correlates with reproductive potential of embryos in women undergoing in vitro fertilization. Fertil Steril 2007; 88: 1350-7. [CrossRef]
2. Sakkas D, Gardner DK. Noninvasive methods to assess embryo quality. Curr Opin Obstet Gynecol 2005; 17: 283-8. [CrossRef]
3. Katz-Jaffe MG, Gardner DK. Symposium: Innovative techniques in human embryo viability assessment. Can proteomics help to change the future of human assisted conception? Reprod Biomed Online 2008; 17: 497-501. [CrossRef]
4. Wong CC, Loewke KE, Bossert NL, Behr B, De Jonge CJ, Baer TM, Reijo Pera RA. Non-invasive imaging of human embryos before embryonic genome activation predicts development to the blastocyst stage. Nat Biotechnol 2010; 28: 1115-21. [CrossRef]
5. Wong C, Chen AA, Behr B, Shen S. Time-lapse microscopy and image analysis in basic and clinical embryo development research. Reprod Biomed Online 2013; 26: 120-9. [CrossRef]
6. Hashimoto S, Kato N, Saeki K, Morimoto Y. Selection of high-potential embryos by culture in poly(dimethylsiloxane) microwells and time-lapse imaging. Fertil Steril 2012; 97: 332-7. [CrossRef]
7. Meseguer M, Herrero J, Tejera A, Hiligsoe KM, Ramsing NB, Remohi J. The use of morphokinetics as a predictor of embryo implantation. Hum Reprod 2011; 26: 2658-71. [CrossRef]
8. Lemmen JG, Agerholm I, Ziebe S. Kinetic markers of human embryo quality using time-lapse recordings of IVF/ICSI-fertilized oocytes. Reprod Biomed Online 2008; 17: 385-91. [CrossRef]
9. Dal Canto M, Coticchio G, Mignini Renzini M, De Ponti E, Novara PV, Brambillasca F, et al. Cleavage kinetics analysis of human embryos predicts development to blastocyst and implantation. Reprod Biomed Online 2012; 25: 474-80. [CrossRef]
10. Sundvall L, Ingerslev HJ, Knudsen UB, Kirkegaard K. Inter- and intra-observer variability of time-lapse annotations. Hum Reprod 2013; 28: 3215-21. [CrossRef]
11. Meseguer M, Rubio I, Cruz M, Basile N, Marcos J, Requena A. Embryo incubation and selection in a time-lapse monitoring system improves pregnancy outcome compared with a standard incubator: A retrospective cohort study. Fertil Steril 2012; 981 481-9.
12. Papanikolaou EG, Camus M, Kolibianakis EM, Van Landuyt L, Van Steirteghem A, Devroey P. In vitro fertilization with single blastocyst-stage versus single cleavage-stage embryos. N Engl J Med 2006; 354: 1139-46. [CrossRef]
13. Blake D, Farquhar C, Johnson N, Proctor M. Cleavage stage versus blastocyst stage embryo transfer in assisted reproductive technology. Cochrane Database Syst Rev 2007; CD002118.
14. Niemitz EL, Feinberg AP. Epigenetics and assisted reproductive technology: A call for investigation. Am J Hum Genet 2004; 74: 599-609. [CrossRef]
15. Manipalviratn S, DeCherney A, Segars J. Imprinting disorders and assisted reproductive technology. Fertil Steril 2009; 91: 305-15. [CrossRef]
16. Basile N, Morbeck D, Garcia-Velasco J, Bronet F, Meseguer M. Type of culture media does not affect embryo kinetics: a time lapse analysis of sibling oocytes. Hum Reprod 2013; 28: 634-41. [CrossRef]
17. Ciray HN, Aksoy t , Goktas C, Ozturk B, Bahceci M. Time-lapse evaluation of human embryo development in single versus sequential culture media--a sibling oocyte study. J Assist Reprod Genet 2012; 29: 891-900. [CrossRef]
18. Kirkegaard K, Hindkjaer JJ, Ingerslev HJ. Effect of oxygen concentration on human embryo development evaluated by time-lapse monitoring. Fertil Steril 2013; 99: 738-44. [CrossRef]
19. Wale PL, Gardner DK. Time-lapse analysis of Mouse embryo development in oxygen gradients. Reprod Biomed Online 2010; 21: 402-10. [CrossRef]

The role of perivitelline space abnormalities of oocytes in the developmental potential of embryos

Hikmet Hassa, Yunus Aydın, Fulya Taplamacıoğlu

Department of Obstetrics and Gynecology, Eskişehir Osmangazi University Faculty of Medicine, Eskişehir, Turkey

Abstract

Objective: In assisted reproductive technology (ART), high embryo quality is closely related to high-quality oocytes. Cytoplasmic maturation and extracytoplasmic maturation are the most important components in determining oocyte quality. One of the most important components of extracytoplasmic maturation is perivitelline abnormalities. The aim of this study is to determine the effect of perivitelline abnormalities on the development of high-quality embryos.

Material and Methods: The study material consisted of 217 of 1154 oocytes from 98 intracytoplasmic sperm injection (ICSI) cycles undertaken due to male factor infertility. Only cycles with long gonadotropin-releasing hormone analogs combined with recombinant Follicle-stimulating hormone (rec-FSH) were included in study. We compared 105 metaphase-II oocytes that had dominantly perivitelline space abnormalities (large perivitelline space with or without granules) with 112 normal metaphase-II oocytes, based on the embryo grade determined by Alpha Scientists in Reproductive Medicine and the European Society of Human Reproduction and Embryology (ESHRE) Special Interest Group of Embryology. Normal metaphase-II oocytes were characterized by a round, clear zona pellucida; a small perivitelline space containing a single unfragmented first polar body; and a pale, moderately granular cytoplasm with no inclusions.

Results: The development rates of Grade I, II, and III embryos were 68.5%, 23.8%, and 7.7%, respectively, in the 105 oocytes with perivitelline abnormalities. The development rates of Grade I, II, and III embryos were 82.1%, 17.9%, and 0%, respectively, in the 112 morphologically normal oocytes. When compared with normal oocytes, Grade I (68.5% vs. 82.1%, p value; 0.019) and Grade III (7.7% vs. 0%, p value; 0.003) embryo development rates were significantly lower in oocytes that had perivitelline abnormalities.

Conclusion: It is important to analyze oocyte quality using multiple parameters, including the perivitelline space. Perivitelline space abnormalities might negatively affect embryo development in male factor-infertile couples that are stimulated with rec-FSH. Therefore, when choosing embryos for transfer, we must take into consideration the historical oocyte data. (J Turk Ger Gynecol Assoc 2014; 15: 161-3)

Key words: Embryo, oocyte, perivitelline space

Received: 07 May, 2014 **Accepted:** 01 July, 2014

Introduction

Assisted reproductive technology (ART) treatment success almost always depends on multiple factors. Every step of the ART affects pregnancy development. Thus, from folliculogenesis to embryo transfer, all steps of ART should be investigated to improve pregnancy rates.

Oocyte quality, which is dependent on oocyte maturity, also plays a major role in the development potential of the embryo (1). There are two components of maturity-nuclear maturity and cytoplasmic maturity-and both components must occur in a coordinated and well-synchronized manner. It is generally recognized that a high-quality oocyte must complete nuclear maturity (M-II oocyte) and should have a round-clear zona pellucida, a small perivitelline space containing a single-non fragmented normal-sized first polar body, and a pale, moderately granular cytoplasm with no vacuoles, and a smooth endoplasmic reticulum (2, 3). However, in addition to the factors that affect oocyte quality, controlled ovarian stimulation protocols are also important.

Even though oocyte morphological scoring is not yet uniform, ESHRE offers an evaluation of every oocyte with uniform parameters to facilitate the delivery of optimal embryos on day 3 or day 5. The most important criteria for oocyte morphology are the following: cumulus-oocyte complex scoring; zona pellucida scoring; perivitelline space abnormalities, such as dilatation or granularity; polar body scoring; cytoplasmic scoring; and vacuolization (4).

Perivitelline space abnormalities are among the most important dysmorphisms of the extracytoplasmic component. It has been reported that a large perivitelline space may be associated with increased oocyte degeneration (5) and lower fertilization rates (6). However, studies have failed to find a correlation between the size and shape of the perivitelline space and fertilization rate or embryo development (1, 7).

In the present study, we evaluated the differences in the development of grade I embryos in normal oocytes and in oocytes with a large perivitelline space.

Address for Correspondence: *Yunus Aydın, Department of Obstetrics and Gynecology, Eskişehir Osmangazi University Faculty of Medicine, Eskişehir, Turkey. Phone: +90 533 516 87 40 e.mail: aydin.yunus@yahoo.com*

DOI:10.5152/jtgga.2014.13091

Material and Methods

The study material consisted of 217 of 1154 oocytes from 98 ICSI cycles undertaken due to male factor infertility in the period from May 2010 to May 2013. Institutional Review Board (IRB) approval was obtained for the study and informed consent form obtained from all couples. Only cycles with long gonadotropin-releasing hormone (GnRH) analogs combined with recombinant Follicle-stimulating hormone (rec-FSH) were included in the study. Oocyte retrieval was performed 36 hours after recombinant human chorionic gonadotropin injection. A total of 250 mcg of recombinant-Human chorionic gonadotropin (rec-hCG) was administered when at least 2-3 follicles with a diameter >18 mm developed. Approximately 2-4 hours after retrieval, oocytes were incubated with 80 IU/mL hyaluronidase for 20-30 sec. Then, cumulus-corona cells were stripped of the follicle with gentle pipetting. The morphology of the oocyte was examined with an inverted microscope at 200x or 400x magnification. The specifications of the first polar body, the perivitelline space, characteristics of the zona pellucida, and the cytoplasmic texture were assessed. A total of 105 oocytes with a perivitelline space abnormality (large perivitelline space with or without granules) (Figure 1) were compared with 112 oocytes that appeared normal (Figure 2) according to the day 3 Grade I, Grade II, and Grade III embryo development potentials. Embryology grading was performed according to the Alpha Scientists in Reproductive Medicine and European Society of Human Reproduction and Embryology (ESHRE) Special Interest Group of Embryology (4) as follows: Grade I embryos were defined as embryos with <10% fragmentation, stage-specific cell size and no multinucleation; Grade II embryos were defined as embryos with 10%-25% fragmentation, stage-specific cell size for the majority of cells, and no multinucleation; and Grade III embryos were defined as embryos with >25% fragmentation, cell size not stage-specific, and presence of multinucleation. From 1154 oocytes, 937 oocytes were excluded from the study, and the exclusion criteria were: i) presence of extracytoplasmic abnormalities in addition to or other than perivitelline abnormality, ii) presence of cytoplasmic abnormalities, iii) oocytes obtained from cycles other than GnRH analogs combined with rec-FSH, and iv) oocytes that were unable to develop day 3 embryos. So, the primary aim was to evaluate the effect of perivitelline abnormalities exclusively on embryo development potential.

IBM SPSS 20 program was used for the statistical analysis (Statistical Package for Social Science, IBM SPSS Inc., Chicago, IL, USA). The differences between the groups were investigated with the two-proportion test, and Pearson chi-square test was used. A p-value <0.05 was considered statistically significant.

Results

A total of 105 oocytes with perivitelline abnormalities were compared to 112 normal oocytes according to the embryo development potential. According to the inclusion criteria, 105 oocytes had no additional cytoplasmic and extra-cytoplasmic abnormality besides perivitelline abnormality; 112 oocytes were totally normal according to the cytoplasmic and extra-cytoplasmic evaluation.

The Grade I, II, and III embryo development rates were 68.5%, 23.8%, and 7.7%, respectively, in the 105 oocytes mainly with a perivitelline abnormality. The Grade I, II, and III embryo development rates were 82.1%, 17.9%, and 0%, respectively, with the 112 morphologically normal oocytes. The Grade I (68.5% vs. 82.1%, p value; 0.019) embryo development rate was significantly lower, and the Grade III (7.7% vs. 0%, p=0.003) embryo development rate was significantly higher in oocytes that had a perivitelline abnormality compared to normal oocytes (Table 1).

Figure 1. A metaphase II oocyte with perivitelline space abnormalities (large perivitelline space with granules)

Figure 2. A normal metaphase II oocyte with round-clear zona pellucida, a small perivitelline space containing a single-non fragmented normal-sized first polar body, and a pale, moderately granular cytoplasm

Discussion

The present study demonstrated a significant relationship between perivitelline space abnormalities and the embryo quality of day 3 embryos. The development rate of Grade I embryos was significantly higher in normal oocytes (no cytoplasmic and extracytoplasmic abnormalities) than in oocytes with perivitelline space abnormalities.

Perivitelline space abnormalities (large perivitelline space with or without granules) are among the most important extracy-

Table 1. Grade I, II, and III embryo development rates in oocytes with perivitelline abnormality and normal oocytes

	Oocytes with perivitelline abnormality (n=105)	Normal oocytes (n=112)	p value
Grade I embryo development, n (%)	72 (68.5)	92 (82.1)	0.019
Grade II embryo development, n (%)	25 (23.8)	20 (17.9)	0.280
Grade III embryo development, n (%)	8 (7.7)	0 (0)	0.003

toplasmic dysmorphisms of the oocyte, but we still we do not understand the exact mechanism of these abnormalities (8). Additionally, it is not clear if the abnormality is physiological or pathological in nature. Some perivitelline space granules are the remnants of coronal cell processes that usually withdraw as the oocyte undergoes resumption of meiosis (9).

The importance of perivitelline space abnormalities is more challenging in ART cycles. Hassan et al. (10) found an association between the granularity of the perivitelline space and lower numbers of MII oocytes; however, perivitelline space granularity was not associated with fertilization rate, cleavage rate, and embryo quality. Interestingly, they found that granularity was positively associated with the dosage of human menopausal gonadotropins administered during stimulation. However, in a study by Rienzi et al. (11), a large perivitelline space was found to be one of the most significant factors associated with lower fertilization rate and pronuclear morphology. In contrast to the study of Hassan et al. (10), Rienze et al. (11) reported the results of patients who underwent ovarian stimulation with rec-FSH. We also demonstrated the negative effect of perivitelline space abnormality on embryo development in a patient that had stimulation with rec-FSH. Therefore, the association of perivitelline space abnormality and HMG, as proposed by Hassan et al. (10), is questionable. Probably, the development of perivitelline space abnormality may not be dependent on the type of gonadotropins, whether HMG or rec-FSH is used.

However, different studies have failed to find a correlation between perivitelline space abnormalities and ART treatment prognosis (2, 12). Moreover, Balaban et al. (2) reported that in couples undergoing ICSI, cytoplasmic abnormalities or extracytoplasmic abnormalities (including perivitelline space) were not associated with decreased fertilization rate or unfavorable embryo quality.

In our study, it was important to study oocytes that mainly had a perivitelline space abnormality. Therefore, the contribution of other cytoplasmic and extracytoplasmic abnormalities to the results was minimal. To the best of our knowledge, Hassan et al. (10) are the only researchers to investigate the role of perivitelline space abnormalities exclusively. However, their study population had undergone ART treatment with HMG. This point is also one of the most important limitations of our study-our results may only be limited to patients who had ovarian stimulation with rec-FSH. Additionally, future studies investigating the association of perivitelline space abnormality with clinical pregnancy rates would be more informative.

In conclusion, oocytes must be evaluated according to multiple parameters, including an analysis of the perivitelline space. Perivitelline space abnormalities might negatively affect embryo development in at least infertile couples with male factor infertility that are stimulated with rec-FSH. Therefore, when choosing embryos for transfer, we must take into consideration the historical oocyte data.

Ethics Committee Approval: *Ethics committee approval was received for this study from Institutional Review Board.*

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

Peer-review: *Externally peer-reviewed.*

Author contributions: *Concept - F.T., Y.A.; Design - F.T.; Supervision - H.H., Y.A.; Resource - F.T.; Materials - F.T.; Data Collection&/or Processing - H.H., Y.A.; Analysis&/or Interpretation - H.H., Y.A., F.T.; Literature Search - Y.A.; Writing - Y.A.; Critical Reviews- H.H., Y.A., F.T.*

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

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

References

1. Ebner T, Moser M, Tews G. Is oocyte morphology prognostic of embryo developmental potential after ICSI? Reprod Biomed Online 2006; 12: 507-12. [CrossRef]
2. Balaban B, Urman B. Effect of oocyte morphology on embryo development and implantation. Reprod Biomed Online 2006; 12: 608-15. [CrossRef]
3. Ebner T, Yaman C, Moser M, Sommergruber M, Feichtinger O, Tews G. Prognostic value of first polar body morphology on fertilization rate and embryo quality in intracytoplasmic sperm injection. Hum Reprod 2000; 15: 427- 30. [CrossRef]
4. Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology. The Istanbul consensus workshop on embryo assessment: proceedings of an expert meeting. Hum Reprod 2011; 26: 1270-83. [CrossRef]
5. Mikkelsen AL, Lindenberg S. Morphology of in-vitro matured oocytes: Impact on fertility potential and embryo quality. Hum Reprod 2001; 16: 1714-8. [CrossRef]
6. Plachot M, Selva J, Wolf JP, Bastit P, de Mouzon J. [Consequences of oocyte dysmorphy on the fertilization rate and embryo development after intracytoplasmic sperm injection. A prospective multicenter study]. Gynecol Obstet Fertil 2002; 30: 772-9. [CrossRef]
7. Balaban B, Urman B, Sertac A, Alatas C, Aksoy S, Mercan R, Nuhoglu A. Oocyte morphology does not affect fertilization rate, embryo quality and implantation rate after intracytoplasmic sperm injection. Hum Reprod 1998; 13: 3431-3. [CrossRef]
8. Tilly JL. Apoptosis and ovarian function. Rev Reprod 1996; 1: 162-172. [CrossRef]
9. Sathananthan AH. Ultrastructure of the human egg. Hum Cell 1997; 10: 21-38.
10. Hassan-Ali H, Hisham-Saleh A, El-Gezeiry D, Baghdady I, Ismaeil I, Mandelbaum J. Perivitelline space granularity: a sign of human menopausal gonadotrophin overdose in intracytoplasmic sperm injection. Hum Reprod 1998; 13: 3425-30. [CrossRef]
11. Rienzi L, Ubaldi F, Iacobelli M, Romano S, Minasi G, Ferrero S, et al. Significance of morphological attributes of the early embryo. Reprod Biomed Online 2005; 10: 669-81. [CrossRef]
12. De Sutter P, Dozortsev D, Qian C, Dhont M. Oocyte morphology does not correlate with fertilization rate and embryo quality after intracytoplasmic sperm injection. Hum Reprod 1996; 11: 595-7. [CrossRef]

What is the importance of omental metastasis in patients with endometrial cancer?

Taner Turan[1], Işın Üreyen[1], Alper Karalök[1], Tolga Taşçı[1], Hilal Ilgın[1], Levent Keskin[2], M. Faruk Kose[1], Gökhan Tulunay[1]

[1]Department of Gynecologic Oncology, Etlik Zübeyde Hanım Women's Health Teaching and Research Hospital, Ankara, Turkey

[2]Department of Gynecology and Obstetrics, Ankara Atatürk Education and Research Hospital, Ankara, Turkey

Abstract

Objective: To identify surgico-pathologic factors, survival, and the factors determining survival in patients with omental metastasis from endometrial cancer.

Material and Methods: Patients with endometrial cancer operated on between 1993-2012 in our hospital and who had omental metastases were included. Patients with either uterine sarcoma or synchronous tumors were excluded.

Results: Omentectomy was performed in 811 patients with endometrial cancer, and omental metastasis was found in 48 (5.9%) patients. Tumor type was endometrioid cancer in 26 patients. Omental metastasis was macroscopic and microscopic in 60% and 40% of the patients, respectively. Total omentectomy increased the chance of detection of the microscopic metastases. Among the patients with omental metastasis, 68.8% had positive peritoneal cytology, 66.7% had adnexal involvement, 60.5% had metastases in the lymph nodes, 47.9% had cervical involvement, and 29.2% had serosal involvement; 43.8% of these patients had intra-abdominal spread beyond the omentum, adnexa, and peritoneal cytology. Two-year disease-free survival (DFS) was 28.2%, and 2-y overall survival (OS) was 40%. The depth of myometrial invasion, grade, cytology, and status of pelvic lymph nodes affected 2-y DFS, while cervical invasion and cytology affected 2-y OS.

Conclusion: Omental metastasis in endometrial cancer means poor prognosis, and two-thirds of these patients are lost at the end of the second year. Although total omentectomy increases the chance of the detection of micrometastases, its effect on survival is controversial. New treatment modalities are necessary in this patient group. (J Turk Ger Gynecol Assoc 2014; 15: 164-72)

Key words: Endometrial cancer, omental metastases, survival

Received: 03 June, 2014 **Accepted:** 25 July, 2014

Introduction

Endometrial cancer is usually diagnosed in the early stages (1). The annual report of the International Federation of Gynecology and Obstetrics (FIGO) revealed that only 3% of newly diagnosed patients had stage IV disease (2). Nevertheless, stage IV disease is responsible for more than half of disease-specific mortality (3).

The extent of surgery in patients with this tumor is still controversial, although it has been staged surgically in accordance with the recommendation of FIGO since 1988. This controversy was about the necessity of routine lymphadenectomy in the staging procedure. Nevertheless, this uncertainty in lymphadenectomy has been pretty much removed with the ASTEC trial (4). This and similar trials showed that lymphadenectomy in addition to total abdominal hysterectomy and bilateral salpingo-oophorectomy does not improve survival in patients with early-stage endometrial cancer (4, 5). Additionally, pelvic and para-aortic lymphadenectomy increases surgical morbidity (6, 7), whereas whether sampling or systemic lymphadenectomy should be performed when lymphadenectomy is necessary, whether the para-aortic region should be involved, and, if involved, the upper level of para-aortic lymphadenectomy (inferior mesenteric artery or left renal vein) are not well defined.

Omentectomy is another controversy of the staging surgery performed in endometrial cancer. Omentectomy is not thought to add morbidity to the surgery, in contrast to lymphadenectomy (8). In addition, the information obtained from this procedure may help in the management. Omental metastasis is observed in 2.4%-8.3% of patients with endometrium cancer (8-15). Nevertheless, it is not clear who to perform omentectomy on and whether omentectomy should be performed for patients without intra-abdominal disease and without high risk factors for metastasis and recurrence. Furthermore, it is not clear how to perform omentectomy in patients without macroscopic metastases in terms of the extent of the procedure (total or infracolic omentectomy, or random biopsy). Additionally, the number of sections that should be taken for the pathologic evaluation of the omentectomy specimen is another enigma.

In the literature, patients with omental metastasis have been presented in studies that analyzed heterogeneous groups

Address for Correspondence: *Işın Üreyen, Department of Gynecologic Oncology, Etlik Zübeyde Hanım Women's Health Teaching and Research Hospital, Ankara, Turkey. Phone: +90 312 322 01 80 e.mail: isin.ureyen@gmail.com*

DOI:10.5152/jtgga.2014.13109

of patients involving all stage IV patients. Patients without other intra-abdominal metastases and patients with microscopic omental metastases were included in these studies. The reports, except the studies mentioned above, were presented as very small case series or case reports. The patients with omental metastases were not analyzed with regard to surgico-pathologic characteristics and survival, and the factors determining survival have not been identified sufficiently in endometrial cancer.

In this study, the determination of surgico-pathologic factors, survival, and the factors determining survival in patients with omental metastases from endometrial cancer is aimed.

Material and Methods

Study Population

The records and pathologic reports of patients with endometrial cancer who were operated in our clinic between 1993 and 2012 were analyzed retrospectively. The patients with omental metastasis were included. Patients with uterine sarcoma, endometrioid carcinoma involving a sarcoma component, or synchronous tumors were excluded. The data related to demographic characteristics, intraoperative findings, debulking status, surgico-pathologic results, patients' treatments, success of their treatments, recurrence and the site of recurrence, and survival were collected from the hospital records. Ethics Committee Approval was taken from the local committee of our institution. Debulking status was obtained from the operative note written by the surgeon.

Patients were staged according to the 2009 FIGO criteria. Patients were evaluated with routine biochemistry, complete blood count, and lung X-ray before the operation. Abdominal and thoracic imaging and Ca-125 were not performed routinely. Staging surgery is performed in our clinic for patients whose frozen section analysis reveals a tumor type other than endometrioid adenocarcinoma, grade 2 or grade 3 disease, myometrial invasion ≥1/2, cervical invasion, and tumor size greater than 2 cm. Furthermore, the patients with a preoperative pathologic diagnosis of high-risk cell type or grade 3 disease are staged directly. Staging surgery involves total abdominal hysterectomy, bilateral salpingo-oophorectomy, systematic pelvic and para-aortic lymphadenectomy, cytology, and omentectomy as a standard. Omentectomy was performed as total, infracolic, or omental biopsy according to the cell type, intraoperative examination, and decision of the surgeon. Cytoreductive surgery was performed in addition to staging surgery in case there was macroscopic disease intraoperatively. Maximal debulking was defined as no gross residual tumor after primary or recurrence surgery, and optimal and suboptimal debulking was used for patients with residual tumor ≤1 cm and >1 cm, respectively.

Adjuvant treatment following surgery and treatment for recurrent disease were defined in accordance with the World Health Organization criteria (16). According to this, clinical response was defined as follows: complete clinic response was clinical disappearance of gross tumor, partial clinical response was a 50% or more reduction in tumor size, stable disease was a 50% or less reduction in tumor size or less than 25% increase in tumor size, and progressive disease was defined as an increase in tumor size more than 25% or appearance of a new tumor.

Follow-up

One month after adjuvant treatment, patients were evaluated with a gynecologic examination and abdominal computerized tomography in order to define the response to the treatment. The patients with complete clinical response were examined every 3 months in the first 2 years, every 6 months in the following 3 years, and then once every year. This assessment included vaginal examination, abdominal ultrasonography, complete blood count, and biochemistry. Lung X-ray was performed every year and additionally, in case there was clinical suspicion. When necessary, thoracic computerized tomography was used. Pap smear and Ca-125 were not used routinely. Patients without complete clinical response were evaluated again, and their treatment was re-planned.

For the pathologic examination of the omentum, sections from the macroscopic tumor or problematic regions were evaluated. Three to 5 sections were taken randomly from the normal-appearing omentum.

Disease-free survival (DFS) was defined as the period between the time of surgery and the observation of the recurrence. Overall survival (OS) was the time between the surgery and death, and follow-up time was evaluated as the time between the surgery and the time that the patient was last examined (death or last visit). We defined recurrence distal to the pelvic inlet (true pelvis), recurrence between the pelvic inlet and diaphragm, and the rest of the recurrences as pelvic recurrence, upper abdominal recurrence, and extra-abdominal recurrence, respectively. We accepted ascites and peritonitis carcinomatosa as upper abdominal recurrence, while we accepted recurrence in the liver parenchyma, skin, and bone as extra-abdominal recurrence.

Statistical Analysis

Statistical data were analyzed by the Statistical Package for Social Sciences (SPSS) 16.0 program working under the Windows XP operative system. Chi-square and Anova table tests were used to analyze the differences between mean values and percentages. Log-rank test was used for univariate analysis. Multivariate analysis could not be performed because of the limited number of patients in the study population. Kaplan-Meier method was used for the analysis of survival. Statistical significance was considered at $p<0.05$.

Results

A total of 1576 patients with endometrial cancer were operated on between 1993 and 2012 in our clinic. Omentectomy was performed in 811 of these patients. Omentectomy was performed as total omentectomy in 70 patients and as infracolic omentectomy in 257 patients, and omental biopsy was carried out in 370 patients. There was no information regarding omentectomy for 113 patients. Omental metastasis was found in 48 (5.9%) patients.

Overall Clinical and Surgico-pathologic Features

At initial diagnosis, the mean age of 48 patients with omental metastasis was 58.6 years, ranging between 31 and 80 years. The preoperative Ca-125 levels of 23 patients could be obtained. The mean Ca-125 was 262 IU/ml. The clinical and surgico-pathologic characteristics of these patients are presented in Table 1 in detail.

Omentectomy was applied as total omentectomy in 27 patients, as infracolic omentectomy in 19 patients, and as omental biopsy in 2 patients. Metastasis was macroscopic in 29 (60%) patients and microscopic in 19 (40%) patients (Table 1). When the patients with macroscopic disease and the patients for whom the omentectomy type was not recorded were not included, the type of omentectomy (total vs infracolic and biopsy) increased the chance of detecting microscopic metastases (n: 6/53, 11.3% vs n:13/616, 2.1%; p<0.001, respectively).

The most common tumor type was endometrioid tumor, and it was detected in 54.2% of the patients. Tumor type was serous in 25%, clear cell in 12.5%, undifferentiated in 4.2%, and mixed-type in 4.2% of the patients. Grade 3 tumor was observed in 62.5% of the patients (Table 1).

Adnexal spread was detected in 66.7%, and cervical and serosal involvement was seen in 47.9% and 29.2% of the patients, respectively (Table 1). Three patients (6.2%) did not have myometrial invasion. Ascites was observed in 40% of the patients, and there were tumoral cells in 68.8% of the peritoneal cytologies of the patients.

Para-aortic and bilateral pelvic lymphadenectomy was performed in 43 of 48 patients with omental metastases (Table 1). The mean number of removed lymph nodes was 15.3 and 30.5 for the para-aortic and pelvic regions, respectively. In total, 26 patients (60.5%) had lymph node metastases. Nineteen patients (n:19/43, 44.2%) had metastasis in the para-aortic region, and 19 patients (n: 19/43, 44.2%) had tumor in the pelvic region. The mean metastatic lymph node number was 7 for both regions.

The type of omental metastases was not associated with tumor type. Omental metastases were microscopic in 11 (42.3%) and 8 (36.4%) patients with endometrioid and non-endometrioid-type tumors, respectively. Macroscopic tumor was detected in 20% of the patients with grade 1 tumor and in 65% of the patients with grade 2 and 3 tumor. Nevertheless, these differences were not significant (p=0.675, p=0.051, respectively). Furthermore, the type of omental metastases was not associated with the depth of myometrial invasion (<1/2 vs ≥1/2), serosal involvement, lymph node metastases, LVSI, and adnexal spread (p=0.058, p=0.317, p=0.415, p=0.063, p=0.297, respectively).

Maximal debulking was achieved in 40 (83.3%) patients. Surgery was optimal in 5 (10.4%) and suboptimal in 3 (6.2%) patients.

The tumor spread to abdominal structures other than the omentum, adnexa, and peritoneal cytology in 43.8% of the patients. Preoperative extraperitoneal spread was not detected. Twenty-one patients had an appendectomy, and tumoral involvement was seen in the appendix serosa in 14 patients (n:14/48, 29.7%). Three patients had a splenectomy, and metastasis was detected in 2 patients (n:2/48, 4.2%). The patient without metastases had a splenectomy because of surgical trauma. Diaphragmatic spread was observed in 3 patients (n:3/48, 6.2%).

Table 1. Characteristic features

Characteristic features		n/ mean	%/median (range)
Age		58.6	60 (31-80)
Preoperative CA 125 (IU/mL)[a]		262	58 (8-1316)
Tumor type	Endometrioid	26	54.2
	Serous	12	25
	Clear Cell	6	12.5
	Mix	2	4.2
	Undifferentiated	2	4.2
Grade	1	5	10.4
	2	13	27.1
	3	30	62.5
Omentectomy	Total	27	56.2
	Infracolic	19	39.6
	Biopsy	2	4.2
Metastasis to omentum	Microscopic	29	60
	Macroscopic	19	40
Ascites	Negative	19	40
	Positive	29	40
Peritoneal cytology	Negative	14	29.2
	Positive	33	68.8
	Not reported	1	2.1
Adnexal metastasis	Negative	16	33.3
	Positive	32	66.7
Myometrial invasion	No invasion	3	6.2
	<1/2	10	20.8
	≥½ and no serosal invasion	21	43.8
	Serosal invasion	14	29.2
Cervical invasion	Negative	25	52.1
	Glandular	3	6.2
	Stromal	20	41.7
Lymphovascular space invasion	Negative	7	14.6
	Positive	24	50
	Not reported	17	35.4
Lymphadenectomy	Performed	5	10.4
	Not performed	43	89.6
Number of lymph nodes removed	Para-aortic	15.3	15 (1-36)
	Pelvic	30.5	30 (2-70)
Lymph node metastasis	Only para-aortic	19	44.2
	Only pelvic	19	44.2
	Para-aortic and pelvic	26	60.5
Number of metastatic lymph nodes	Para-aortic	7	5 (1-28)
	Pelvic	7	5.5 (1-25)
Intra-abdominal metastasis[b]	Negative	27	56.2
	Positive	21	43.8
Result of primary surgery	Suboptimal debulking	3	6.2
	Optimal debulking	5	10.4
	Maximal debulking	40	83.3

[a]: 23 patients' preoperative Ca-125 levels were available.
[b]: Other than adnexa, peritoneal cytology and omentum

Two patients had diaphragmatic stripping, and argon beam laser was performed in 1 patient for tumoral debulking. Sigmoid colon resection was done for maximal debulking in 2 patients (n:2/48, 4.2%).

Forty-three patients took adjuvant therapy. Two patients did not take adjuvant therapy, since they were lost to follow-up. Palliative treatment was given to 3 patients. Adjuvant therapy was platinum-based chemotherapy for 32 patients. Seven patients took radiotherapy, and 4 patients took sandwich therapy (3 cycles of paclitaxel+carboplatin, followed by interval radiotherapy, followed by 3 cycles of paclitaxel+carboplatin). Four patients taking adjuvant therapy were lost to follow-up during treatment. Clinical complete response was achieved in 30 (n:30/39, 77%) patients, while progression was observed in 7 patients (n:7/39, 18%). During treatment, 2 patients died due to a pulmonary embolism. These deaths were not considered perioperative deaths, since they died after more than 1 month following surgery.

Survival Analysis

While 2 patients refused to take chemotherapy, 4 patients did not complete therapy, 1 patient was lost to follow-up after taking the treatment, and 2 patients died of pulmonary embolism; 9 patients were not included in the survival analysis. DFS analysis was performed with 39 patients. OS analysis was performed with 35 patients, since 1 patient refused to take the treatment after recurrence and 3 patients were lost to follow-up during treatment. The median follow-up time was 15 months, ranging between 1 and 130 months. During follow-up, recurrence was observed in 31 patients (n: 31/39, 79.5%). The mean time to recurrence was 11 months in these patients. The Ca-125 levels of 18 patients with recurrence were known. The mean Ca-125 level of these patients was 200 IU/ml (Table 2).

One of the 31 patients with recurrence refused treatment. Among the 30 patients who took therapy, 14 patients took chemotherapy, 4 patients took chemotherapy following surgery, and 12 patients took palliative treatment. The data on response to treatment in 17 of the 18 patients who took curative therapy were available. Among these 17 patients, progression was observed in 15 patients (n:15/17, 88.2%), since clinical complete response was achieved in 2 patients (n:2/17, 11.8%). These 2 patients were the ones for whom maximal debulking was achieved during surgery that was done for recurrence. One of these patients died of disease 10 months after achieving a clinical complete response. The last status of the second patient was not known, since she was lost to follow-up.

Recurrence was outside of the pelvic region in 21 patients. There was extra-abdominal spread in 18 patients. Among them, 10 patients and 13 patients had recurrence in the lung and liver, respectively; 14 patients had recurrence in the upper abdominal region. Recurrence was only extra-abdominal in 8 patients, only in the upper abdomen in 7 patients, and only in the pelvic region in 5 patients, since 1 patient had recurrence in all three regions. Detailed data related to recurrence are presented in Table 2.

Type of adjuvant therapy was not associated with the region of recurrence. Excluding patients who took sandwich therapy and palliative treatment, 20% of the patients who took radiotherapy had recurrence in the pelvis, since this ratio was 33% for patients in the chemotherapy group. On the other hand, there was extra-abdominal metastasis in 48% and 60% of the patients in the chemotherapy and radiotherapy groups, respectively. Nevertheless, these differences were insignificant (p=0.555, p=0.626, respectively).

Table 2. Characteristic features in recurrence

Characteristic Features		n/ mean	%/median (range)
CA 125 (IU/mL)[1]		200	155 (3-525)
Follow-up (month)		21	15 (1-130)
Recurrence	Negative	8	20.5
	Positive	31	79.5
Disease free survival time in patient with recurrence (month)		11	9 (2-50)
Recurrence site	Only pelvic	5	16.1
	Only upper abdominal	7	22.6
	Only extra-abdominal	8	25.8
	Pelvic+extra-abdominal	4	12.9
	Upper abdominal+ extra-abdominal	6	19.4
	Pelvic+upper abdominal+extra-abdominal	1	3.2
Exitus	Negative	8	23
	Positive	27	77
Overall survival time in patient who dead of disease (month)		18	14 (2-55)

[1]: The data of 18 patients

During the follow-up period, 27 patients (n: 27/35, 77%) died of disease. Mean time to death was 18 months in these patients. At the end of the first year, 56.4% of the patients had recurrence, and at the end of the second year, this ratio became 71.8%. Additionally, 29% and 60% of patients died of disease at the end of the first and second year, respectively. Peritoneal cytology was a prognostic factor for both 2-y DFS and 2-y OS (Figure 1, 2). Additionally, myometrial invasion and grade and status of pelvic lymph nodes were determining factors for 2-y DFS, and 2-y OS was associated with cervical invasion (Table 3). Survival was not affected by the type of omental metastases and existence of other intra-abdominal metastases. Aggressive surgery was not associated with survival statistically. Nevertheless, patients with suboptimal debulking died within 2 years. Patients with maximal debulking had a 20% improvement in 2-y DFS compared to other patients. A decrease in 2-y DFS and 2-y OS was observed in the presence of risk factors. However, this decrease was not significant statistically, since the study population was small and these factors were not distributed proportionately (Table 3).

Discussion

Endometrial cancer metastasizes by direct spread into the myometrium, extending to the cervix, hematogenous dissemination,

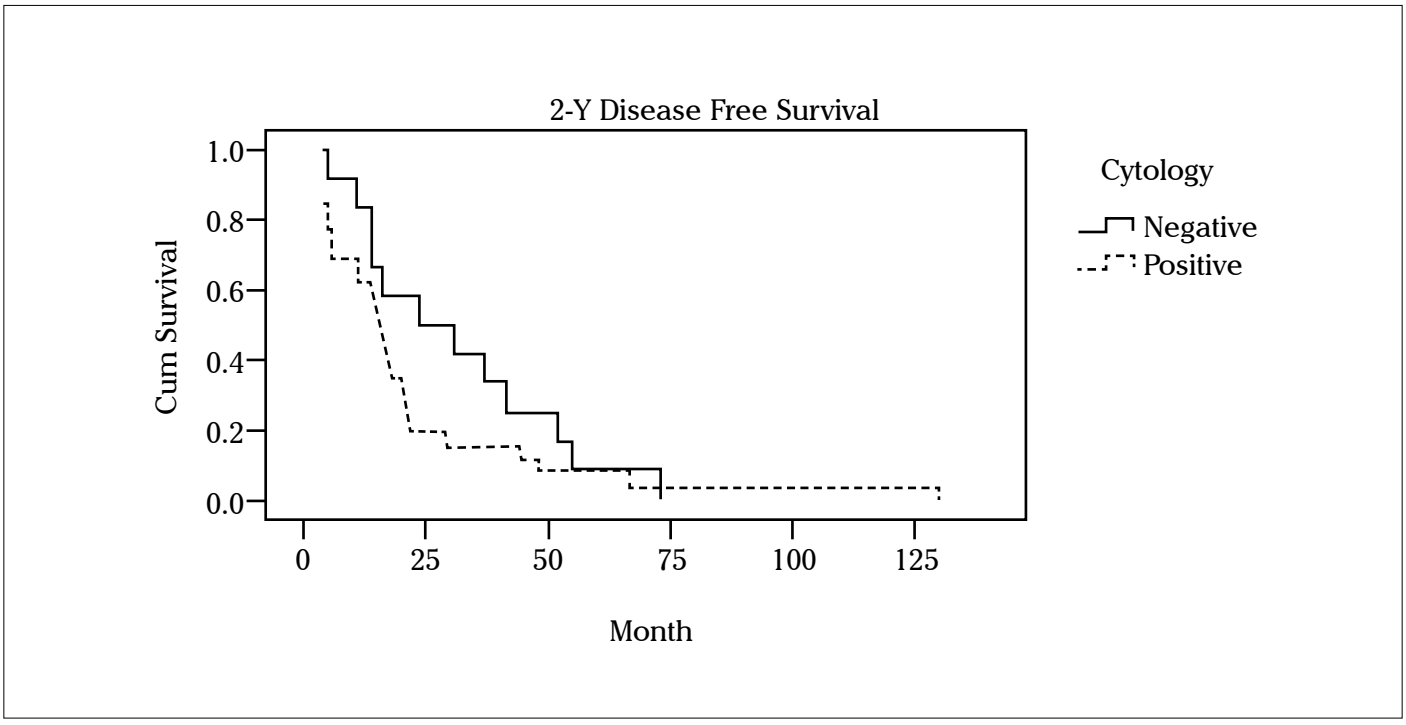

Figure 1. Cytology and 2-y disease-free survival

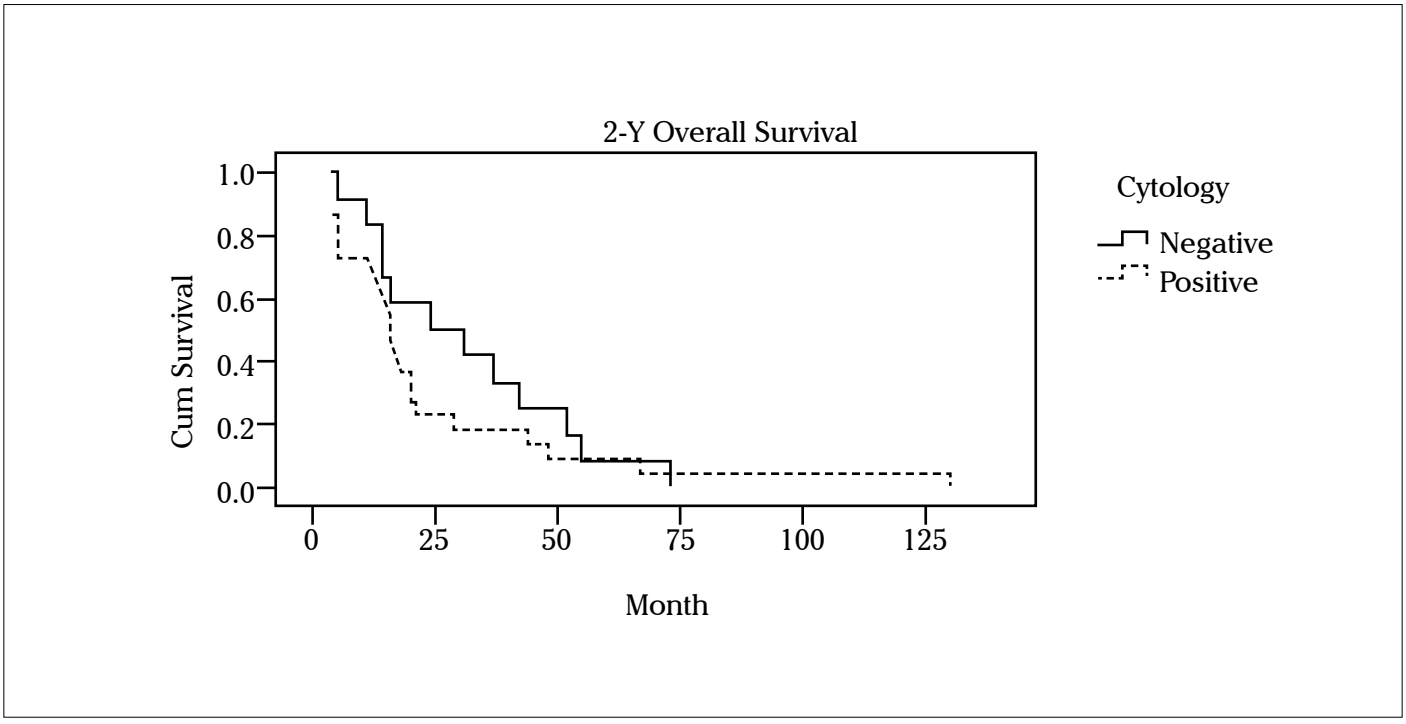

Figure 2. Cytology and 2-y overall survival

lymphatic embolization, and peritoneal seeding (17). Omental spread was thought to occur as a result of peritoneal seeding and regional lymphatics (11). On the other hand, the omentum is most probably a different region for metastases of endometrial tumor cells compared to other regions in the body. Klopp et al. (18) showed that omental adipose tissue, different from other tissues, stimulated the development of endometrial tumor cells and neovascularization. Omental adipose tissue was thought to promote tumor vascularization and survival and proliferation of tumor cells in comparison to subcutaneous adipose tissue.

In this study, the ratio of metastases to the omentum in the group of patients who had an omentectomy was 5.9%. It was 9.1% in

Table 3. The factors determining 2-y disease-free survival and 2-y overall survival in patients with omental metastases. Univariate analysis

		2-year disease-free survival			2-year overall survival		
Parameter		**n/total n**	**%**	**p**	**n/total n**	**%**	**p**
Age	≤60	5/20	25	0.648	7/17	41.2	0.554
	>60	6/19	31.6		5/16	31.2	
Tumor type	Endometrioid	7/19	36.8	0.243	5/15	33.3	0.741
	Non-endometrioid	4/20	20		7/18	38.9	
Grade	1 and 2	6/12	50	0.044	5/11	45.5	0.443
	3	5/27	18.5		7/22	31.8	
Depth of myometrial invasion	<1/2	6/12	50	0.044	5/10	50	0.283
	≥1/2	5/27	18.5		7/23	30.4	
Uterine serosal invasion	Negative	10/27	37	0.066	9/22	40.9	0.443
	Positive	1/12	8.3		3/11	27.3	
Lymphovascular space invasion	Negative	4/7	57.1	0.093	2/5	40	1
	Positive	4/18	22.2		6/15	40	
Cervical invasion	Negative	7/20	35	0.333	9/17	52.9	0.041
	Positive	4/19	21.1		3/16	18.8	
Preoperative ascites	Negative	7/22	31.8	0.568	7/19	36.8	0.947
	Positive	4/17	23.5		5/14	35.7	
Peritoneal cytology	Negative	7/12	58.3	0.007	7/11	63.6	0.027
	Positive	4/26	15.4		5/21	23.8	
Adnexal metastasis	Negative	4/10	40	0.336	3/7	42.9	0.687
	Positive	7/29	24.1		9/26	34.6	
Other intra-abdominal metastasis[a]	Negative	8/22	36.4	0.198	7/21	33.3	0.632
	Positive	3/17	17.6		5/12	41.7	
Type of omentectomy	Infracolic + biopsy	5/17	29.4	0.883	5/16	31.2	0.554
	Total	6/22	27.3		7/17	41.2	
Omental metastasis	Microscopic	5/15	33.3	0.574	5/14	35.7	0.947
	Macroscopic	6/24	25		7/19	36.8	
MicOM vs MacIM	MicOM	4/10	40	0.336	4/10	40	0.775
	MacIM	7/29	24.1		8/23	34.8	
Lymphadenectomy	No	0/3	0	0.258	0/2	0	0.270
	Yes	11/36	30.6		12/31	38.7	
Removed lymph nodes number	≤45	4/15	26.7	0.866	6/14	42.9	0.506
	>45	7/24	29.2		6/19	31.6	
Pelvic lymph node metastasis	Negative	9/20	45	0.035	7/16	43.8	0.552
	Positive	2/16	12.5		5/15	33.3	
Para-aortic lymph node metastasis	Negative	8/20	40	0.169	7/15	46.7	0.379
	Positive	3/16	18.8		5/16	31.2	
Primary cytoreduction	Optimal+Suboptimal	1/8	12.5	0.268	2/6	33.3	0.554
	Maximal	10/31	32.3		10/17	37	
Adjuvant therapy	Chemotherapy	10/28	35.7	0.492	11/22	50	0.223
	Radiotherapy	1/5	20		1/5	20	

[a]: Except for omentum, adnexa, and cytology
MicOM: microscopic omental metastasis; MacIM: macroscopic intra-abdominal metastasis (omental and other intra-abdominal metastasis)

our previous study evaluating mixed-type endometrial carcinoma (19). Similarly, the ratio of omental metastasis in endometrial cancer was reported between 2.4% and 8.3% (8-15). Nevertheless, in these studies, omentectomy was performed as infracolic omentectomy or omental biopsy. Furthermore, 11%-71.4% of the reported omental metastases were micrometastases (8-15, 20). It is not possible to say whether there were microscopic metastases or not in the remaining omentum after subtotal omentectomy. Therefore, in fact, the reported ratios related to omental metastases were minimum figures, and most probably, the ratio of omental metastasis was much higher than the reported numbers. Hence, the factors determining omental metastases were not reviewed in this study.

Data related to whether omental metastases could be detected at a higher ratio with total omentectomy could not be obtained from the literature. In this study, omental micrometastases was shown to be detected 5 times more often with total omentectomy (11.3% vs 2.1%, $p<0.001$). Even if we could detect omental metastases with total omentectomy at a higher ratio, this may not demonstrate the real ratio of omental metastasis. The limitation in the pathologic examination is the reason. Detection of a metastasis of 1 mm in a 33x24 cm omental specimen needs almost 800 sections in the pathologic examination, and this seems almost impossible in clinical practice (9). Therefore, total omentectomy will not solve the problem in the detection of metastasis in the omentum. In conclusion, one can say that the detection of omental micrometastases depends on chance.

In endometrial cancer, the surgico-pathologic characteristics of the patients with omental metastasis have been evaluated in detail. Nevertheless, the reported data belonged to very small groups of patients (maximum n:6). In these studies, patients with omental metastases had high-risk pathologic characteristics at a higher ratio compared to patients of the normal endometrial cancer population, as expected. In the current study, high-risk factors were encountered at a high ratio. Almost half of the patients had nonendometrioid-type tumors, 62.5% of patients had grade 3 disease, 73% had myometrial invasion ≥1/2, 66.7% had adnexal spread, 60.5% had metastases in the lymph nodes, and 48% had cervical invasion (Table 1). While 43.8% of the patients had intra-abdominal spread other than the omentum, adnexa, and peritoneal cytology, there was no patient with extra-abdominal metastases.

We could not reach data in the literature with which we could compare the survival of patients with omental metastasis in endometrial cancer and data related to factors determining survival in these patients. Fujiwara et al. (10) reported that patients with omental metastasis died in 15 months, since Dilek et al. (8) reported that patients with microscopic metastasis died in 36 months and Metindir et al. (12) stated 3-y DFS to be 20% in this patient population. Nevertheless, the number of the cases reported in these studies was 4, 3, and 4, respectively. Therefore, it is not possible to get definite data related to the survival of patients with omental metastasis in endometrial cancer from these studies. In the current study, 1-y DFS and 2-y DFS were 45.4% and 28.2%, respectively; 1-y OS and 2-y OS were 71% and 40%, respectively. Positive peritoneal cytology was a significant prognostic factor for both 2-yDFS and 2-y OS. Additionally, depth of myometrial invasion and grade and status of pelvic lymph nodes were determining factors for 2-y DFS, since presence of cervical invasion was predictive for 2-y OS. Peritoneal cytology is expected to be positive in patients with intra-abdominal spread, including omental metastases, whereas in this study, only 68.8% of patients had tumor cells in the peritoneal fluid. This situation may be explained by the spread of disease via regional lymphatics.

There was no difference between patients with microscopic and macroscopic omental metastasis in terms of survival; 2-y OS was similar for both groups of patients (35.7% vs 36.8%, respectively). However, 2-y DFS was 16% better in cases where there was only microscopic omental metastasis compared to the presence of intra-abdominal macroscopic metastasis (omental and other intra-abdominal metastases). This ratio for 2-y OS was 5% (Table 3). These differences were statistically insignificant ($p=0.336$, $p=0.775$, respectively).

In the presence of factors that were evaluated in the current study and that were found to be statistically insignificant, survival decreased significantly (Table 3). Especially, when the grade increased; when there was uterine serosal involvement, lymphovascular space invasion, adnexal spread, or para-aortic lymph node metastases; and when maximal debulking could not be achieved and radiotherapy was used as the adjuvant treatment, survival decreased. These differences were not statistically significant, since the study group was small and the factors were distributed disproportionately. Although total omentectomy was important for detecting omental micrometastases according to this study, the type of omentectomy was not associated with survival in patients with omental metastasis. However, 2-y OS was 10% better in patients who had a total omentectomy (Table 3).

Survival in the present study may be compared only with the results of studies analyzing patients with stage IVB endometrial cancer. Although stage IVB endometrial cancer includes a heterogeneous group of patients, age, extra-abdominal spread, lymph node metastases, adjuvant therapy, grade, cervical invasion, depth of myometrial invasion, performance status of the patients, and especially aggressive surgery were all reported to determine survival (20-22). In these studies and in a meta-analysis evaluating cytoreductive surgery in patients with primary and recurrent endometrial cancer, extent of surgery was shown to be the main factor determining survival in patients with stage IVB endometrial cancer (20-23). In a study by Bristow et al. (21), patients who had optimal debulking surgery were found to survive 3 times longer than patients for whom optimal debulking could not be achieved. The subgroup analysis of the same study showed that in the optimally debulked group, patients with only microscopic residual disease survived longer than patients with gross disease smaller than 1 cm. Ayhan et al. (22) presented 2-y OS as 30% for patients with stage IVB endometrial cancer for whom 32% maximal debulking and 60% optimal debulking were achieved. In the current study, in which 83.3% maximal debulking was achieved, 2-y OS was 40%. In the patients for whom maximal debulking was achieved, 20% improvement in 2-y DFS was seen. However, the improvement in 2-y OS was only 4%. Additionally, the patients for whom maximal or optimal cytoreduction could not be achieved died within 2 years.

We thought that it was inappropriate to compare the results of this study and studies analyzing patients with stage IVB disease in terms of survival -that is to say, in the current study, there was a 10% difference in 2-y OS in comparison to the study by Ayhan et al. (22). This difference may be explained by the difference in the ratios of maximal debulking, as well as by the inequality between the patient groups. In the study of Ayhan et al. (22), there were extra-abdominal metastases in 16%; liver, spleen, or diaphragmatic spread in 24%; small intestine involvement in 24%; and large intestine involvement in 19% of the patients. Omental metastasis was detected in only half of the patients. As can be seen, tumors were more prevalent in the patient population in the analysis of Ayhan et al. (22) compared to the current study, which evaluated only patients with omental metastasis. It is also inappropriate to compare these results with the Japanese multi-center study evaluating stage IVB endometrial cancer. In the study by Eto et al. (20), 248 patients were analyzed, and only 58% of these patients had omental metastasis, since 38% had extra-abdominal spread. Eventually, the patient population of the current study was limited compared to the patients in the studies analyzing cases with stage IVB endometrial cancer. Consequently, there are no data in the literature that we can directly compare the results of this study with in terms of survival.

There is no standard treatment for stage IVB endometrial cancer with regard to adjuvant therapy. Nevertheless, there is a consensus on the necessity of systemic treatment, since disease in this stage should be accepted as systemic. Eto et al. reported that chemotherapy with or without radiotherapy was a determining prognostic factor for survival (20). Similar results were stated in the study of Ayhan et al. (22). In the Gynecologic Oncology Group study, in which Randall et al. (24) compared whole abdominal radiotherapy with adriamycin and cisplatin combination, survival was shown to improve with chemotherapy in advanced-stage endometrial cancer. It was reported that extra-abdominal recurrence decreased from 19% to 10% with chemotherapy, since local recurrence increased from 13% to 18%. In the current study, it was shown that distant recurrence decreased with chemotherapy, while central recurrences increased. Recurrence in the pelvis was observed in 20% of the patients who took only radiotherapy, since this ratio was 33% for patients who took chemotherapy. On the other hand, 48% of the patients who took chemotherapy and 60% of the patients who took radiotherapy had extra-abdominal metastases. Additionally, compared to radiotherapy, chemotherapy improved 2-y DFS and 2-y OS by 16% and 30%, respectively (Table 3). Nevertheless, these differences were not statistically significant (p=0.492, p=0.223, respectively).

In conclusion, omental metastasis in endometrial cancer is most probably more common than reported. We thought that the omentum should be evaluated surgically in endometrial carcinoma. However, although total omentectomy has a role in the detection of omental micrometastases, its effect on survival in the patients with omental metastasis is not clear. The effect of total omentectomy on survival in patients with endometrial carcinoma and especially in patients without high-risk factors is not known, but it is obvious that it may make a difference. It may help to define the stage and to manage the patient, and additionally, it may provide tumoral debulking of possibly undiagnosed metastases, even if the metastases could not be detected with total omentectomy. Nonetheless, it is not realistic to suggest total omentectomy or to refuse this procedure in patients with endometrial cancer according to the results of this study, evaluating only patients with omental metastasis. In this patient population, aggressive surgery improved survival, although it was not statistically significant. The patients with suboptimal debulking surgery died of disease in 2 years. In these patients, maximal debulking should be the goal of the surgery. Similarly, even though the effect of systemic treatment was statistically insignificant, survival greatly improved with the administration of chemotherapy. The current study is a retrospective study, and although it is the largest series of patients with omental metastasis in endometrial cancer that has been analyzed in detail in the literature, it was too small a series to make definite conclusions in terms of survival. Nevertheless, omental metastasis is a poor prognostic factor in endometrial carcinoma, and two-thirds of these patients died at the end of the second year. Therefore, this patient group is a group in which new treatment modalities should be developed. Patients with omental metastases from endometrial cancer should preferably be treated in multi-center studies.

Ethics Committee Approval: *Ethics committee approval was received for this study from the local committee of the institution.*

Informed Consent: *N/A.*

Peer-review: *Externally peer-reviewed.*

Author contributions: *Concept - T.T.; Design - A.K., T.T.; Supervision - G.T.; Resource - F.K.; Materials - L.K.; Data Collection&/or Processing - H.I., L.K.; Analysis&/or Interpretation - I.Ü.; Literature Search - A.K., T.T.; Writing - T.T., I.Ü.; Critical Reviews - F.K., G.T.*

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

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

References

1. Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, Vergote I. Endometrial cancer. Lancet 2005; 366: 491-505. [CrossRef]
2. Creasman WT, Odicino F, Maisonneuve P, et al. Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obstet 2006; 95 (Suppl 1): S105-43. [CrossRef]
3. Cook AM, Lodge N, Blake P. Stage IV endometrial carcinoma: a 10 year review of patients. Br J Radiol 1999; 72: 485-8. [CrossRef]
4. ASTEC study group, Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): A randomized study. Lancet 2009; 373: 125-36. [CrossRef]
5. Chan JK, Wu H, Cheung MK, Shin JY, Osann K, Kapp DS. The outcomes of 27,063 women with unstaged endometrioid uterine cancer. Gynecol Oncol 2007; 106: 282-8. [CrossRef]

6. Larson DM, Johnson K, Olson KA. Pelvic and para-aortic lymphadenectomy for surgical staging of endometrial cancer: Morbidity and mortality. Obstet Gynecol 1992; 79: 998-1001.
7. Hidaka T, Kato K, Yonezawa R, Shima T, Nakashima A, Nagira K, et al. Omission of lymphadenectomy is possible for low-risk corpus cancer. Eur J Surg Oncol 2007; 33: 86-90. [CrossRef]
8. Dilek S, Dilek U, Dede M, Deveci MS, Yenen MC. The role of omentectomy and appendectomy during the surgical staging of clinical stage I endometrial cancer. Int J Gynecol Cancer 2006; 16: 795-8. [CrossRef]
9. Usubütün A, Ozseker HS, Himmetoglu C, Balci S, Ayhan A. Omentectomy for gynecologic cancer: How much sampling is adequate for microscopic examination? Arch Pathol Lab Med 2007; 131: 1578-81.
10. Fujiwara H, Saga Y, Takahashi K, Ohwada M, Enomoto A, Konno R, et al. Omental metastases in clinical stage I endometrioid adenocarcinoma. Int J Gynecol Cancer 2008; 18: 165-7. [CrossRef]
11. Freij MA, Burbos N, Mukhopadhyay D, Lonsdale R, Crocker S, Nietto JJ. The role of omental biopsy in endometrial cancer staging. Gynecol Surg 2009; 6: 215-53. [CrossRef]
12. Metindir J, Dilek GB. The role of omentectomy during the surgical staging in patients with clinical stage I endometrioid adenocarcinoma. J Cancer Res Clin Oncol 2008; 134: 1067-70. [CrossRef]
13. Saygili U, Kavaz S, Altunyurt S, Uslu T, Koyuncuoglu M, Erten O. Omentectomy, peritoneal biopsy and appendectomy in patients with clinical stage I endometrial carcinoma. Int J Gynecol Cancer 2001; 11: 471-4. [CrossRef]
14. Nieto JJ, Gornall R, Toms E, Clarkson S, Hogston P, Woolas RP. Influence of omental biopsy on adjuvant treatment field in clinical Stage I endometrial carcinoma. BJOG 2002; 109: 576-8. [CrossRef]
15. Chen SS, Spiegel G. Stage I endometrial carcinoma. Role of omental biopsy and omentectomy. J Reprod Med 1991; 36: 627-9.
16. WHO handbook for reporting results of cancer treatment. WHO Offset Publication 1979; No: 148.
17. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. Cancer 1987; 60 (8 Suppl): 2035-41. [CrossRef]
18. Klopp AH, Zhang Y, Solley T, Amaya-Manzanares F, Marini F, Andreeff M, et al. Omental adipose tissue-derived stromal cells promote vascularization and growth of endometrial tumors. Clin Cancer Res 2012; 18: 771-82. [CrossRef]
19. Duzguner S, Ilgin Hilal, Tasci Tolga, Duzguner I, Turan T, Boran N, et al. Analysis of mixed type endometrial carcinoma. J Turk Soc Obstet Gynecol 2014; 2: 119-25.
20. Eto T, Saito T, Kasamatsu T, Nakanishi T, Yokota H, Satoh T, et al. Clinicopathological prognostic factors and the role of cytoreduction in surgical stage IVb endometrial cancer: A retrospective multi-institutional analysis of 248 patients in Japan. Gynecol Oncol 2012; 127: 338-44. [CrossRef]
21. Bristow RE, Zerbe MJ, Rosenshein NB, Grumbine FC, Montz FJ. Stage IVB endometrial carcinoma: the role of cytoreductive surgery and determinants of survival. Gynecol Oncol 2000; 78: 85-91. [CrossRef]
22. Ayhan A, Taskiran C, Celik C, Yuce K, Kucukali T. The influence of cytoreductive surgery on survival and morbidity in stage IVB endometrial cancer. Int J Gynecol Cancer 2002; 12: 448-53. [CrossRef]
23. Barlin JN, Puri I, Bristow RE. Cytoreductive surgery for advanced or recurrent endometrial cancer: a meta-analysis. Gynecol Oncol 2010; 118: 14-8. [CrossRef]
24. Randall ME, Filiaci VL, Muss H, Spirtos NM, Mannel RS, Fowler L, et al. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: A Gynecologic Oncology Group study. J Clin Oncol 2006; 24: 36-44. [CrossRef]

Comparison of serum maternal adiponectin concentrations in women with isolated intrauterine growth retardation and intrauterine growth retardation concomitant with pre-eclampsia

Barış Büke[1], Hasan Onur Topçu[2], Yaprak Engin-Üstün[2], Nuri Danışman[2]

[1]Department of Obstetrics and Gynecology, Ege University Faculty of Medicine, İzmir, Turkey

[2]Department of Obstetrics and Gynecology, Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara, Turkey

Abstract

Objective: The aim of this study was to compare serum maternal adiponectin concentrations in pregnant women with isolated intrauterine growth retardation (IUGR) and in pregnant women with IUGR concomitant with pre-eclampsia (IUGRcwPE).

Material and Methods: Thirty patients with isolated IUGR (group 1), 20 patients with IUGRcwPE (group 2), and 30 healthy controls (group 3) between age 18-40 were included into the study. Venous blood samples of those patients were obtained in the starving state. Adiponectin concentrations were measured by enzyme-linked immunosorbent assay in serum obtained after centrifugation. To find the differences between the groups, student t-test and one-way ANOVA statistical methods were used.

Results: There were no differences between the groups in terms of age, body mass index, gestational age, and parity ($p>0.05$). The values of amniotic fluid index ($p<0.001$) and weight gained during pregnancy ($p=0.017$) were significantly different when compared among the three groups. The mean concentrations of adiponectin were 94.041 pg/mL in the IUGR group, 55.717 pg/mL in the IUGRcwPE group, and 51.831 pg/mL in the control group. Both of the differences between the IUGR and IUGRcwPE groups (p value; <0.05) and IUGR and control groups were statistically significant (p value; <0.001). However, there were no significant differences between the IUGRcwPE group and control group ($p>0.05$).

Conclusion: We found that IUGR increased maternal serum adiponectin concentrations; however, this rise does not occur in pregnant women with IUGRcwPE. (J Turk Ger Gynecol Assoc 2014; 15: 173-6)

Key words: IUGR, pre-eclampsia, adiponectin

Received: 01 July, 2014 **Accepted:** 25 July, 2014

Introduction

Adiponectin, which was first isolated from adipose tissue by Maeda et al. (1) in 1996, has become a mysterious and interesting substance since its first description. It has been thought to inhibit vascular inflammation, improve insulin sensitivity, and have antiatherogenic effects (2).

Some clinical studies showed an association between serum adiponectin concentration and obesity (3-5). A low level of plasma adiponectin concentrations in obese humans and a positive correlation between adiponectin concentrations and insulin sensitivity were shown in another study (6).

Intrauterine growth retardation (IUGR) is described as a fetus whose weight is less than expected based on gestational age and sex, as determined by population standards; frequently chosen cut-off points are below the 10th percentile on these curves (7). Pre-eclampsia refers to the new onset of hypertension and proteinuria after 20 weeks of gestation in a previously normotensive woman (8). Adiponectin receptors are found abundantly in placenta (9). In many studies, maternal serum adiponectin concentrations were constant or decreased during the pregnancy. The unchanged situation of serum adiponectin concentrations were commented on as an independent protective reflex against increased insulin resistance (10-13); however, the decreased adiponectin concentrations were explained by the decreased insulin sensitivity during pregnancy (14, 15). A decline in maternal serum adiponectin concentrations in IUGR and reduced plasma adiponectin concentrations were shown in past studies (16, 17).

Here, we conducted this present study to compare serum adiponectin concentrations in women with isolated IUGR and in women with IUGR concomitant with pre-eclampsia (IUGRcwPE).

Address for Correspondence: *Hasan Onur Topçu, Department of Obstetrics and Gynecology, Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara, Turkey. Phone: +90 532 635 95 38 e.mail: dronurtopcu@gmail.com*

DOI:10.5152/jtgga.2014.13130

Material and Methods

This case-control study was conducted at Zekai Tahir Burak Women's Health Education and Research Hospital in Ankara, Turkey. A total of 80 pregnant women, ages 18 to 40 years, and ones who had more than 28 gestational weeks were enrolled into the study. The pregnant women were classified as having isolated IUGR, IUGRcwPE, and healthy controls. The first group consisted of 30 pregnant women with isolated IUGR, the second group consisted of 20 pregnant women with IUGRcwPE, and the control group consisted of 30 healthy pregnant women. The exclusion criteria were maternal systemic illness, multifetus pregnancies, structural or chromosomal anomalies, and smoking pregnant women. The study was approved by the ethical committee and institutional review board of Zekai Tahir Burak Women's Health Education and Research Hospital, and written informed consent was obtained from each participant.

Gestational age (weeks) was assessed by ultrasound examination (Logiq 200 PRO Ultrasound Device; GE Medical Systems, Milwaukee, USA) or according to the last menstrual period, or both. The pregnant women who had estimated fetal weights according to the Hadlock Formula (18) that were below the 10th percentile for gestational age formed the isolated IUGR group. The pregnant women who had IUGR and pre-eclampsia formed the IUGRcwPE group. The pregnant women who had estimated fetal weights according to the Hadlock formula (18) that were at or above the 10th percentile formed the control group. The diagnosis of pre-eclampsia was corrected with the new onset of hypertension and proteinuria after 20 weeks of gestation in a previously normotensive woman.

Fasting blood samples were obtained from the antecubital vein in the third trimester. The samples were centrifuged for 10 minutes at 4000 revolutions per minute and then were stored at -80°C. Plasma adiponectin concentrations were measured by using the human adiponectin ACRP30 ELISA kit (EZHADP-61K; Merck Millipore, Massachusetts, USA).

Statistical analysis was performed using Statistical Package for Social Sciences version 14.0 (SPSS; Chicago, IL, USA). The descriptive statistical methods (mean, standard deviation, median) and the comparison of quantitative data were performed using student's t-test and one-way ANOVA. The confidence interval was 95%, and $p<0.05$ was considered a statistically significant difference among the groups.

Results

The descriptive characteristics of the women are shown in Table 1. There was no significant difference among the groups in terms of maternal age, gravidity, parity, miscarriage, body mass index (BMI), and gestational age ($p>0.05$).

The median of the ultrasonography measurement of abdominal circumference of the fetuses was 31.6±3.22 weeks in the IUGR group, 28.7±2.92 weeks in the IUGRcwPE group, and 35.19±3.3 weeks in the control group ($p<0.0001$). The mean of the amniotic fluid index (AFI) was 52.1 cm in the IUGR group, 39.3 cm in the IUGRcwPE group, and 108.6 cm in the control group. The differences among the groups were statistically significant ($p<0.001$). The mean of the BMI among the groups was not statistically significant ($p=0.731$); however, the weight gain was 9.19±4.53 kg in the IUGR group, 10.2±2.6 kg in the IUGRcwPE group, and 12.23±6.34 kg in the control group. The differences of weight gain between the IUGR and control groups were statistically significant ($p=0.017$).

Table 1. The characteristics of the study population

	IUGR n=30	IUGR+PE n=20	Control n=30	P values
Age (year)	27.23±5.981	26.45±5.196	26.58±4.726	0.852
Gravidity	2.20±1.186	2.16±1.522	2.04±1.183	0.892
Parity	1.03±1.098	0.84±1.214	0.69±0.884	0.487
Systolic Blood Pressure (mm Hg)	112.1±4.9	156±13	111.7±7.3	<0.001
Diastolic Blood Pressure (mm Hg)	71.21±2.9	100.4±8.44	72.5±5.1	<0.001
Proteinuria (g/day)	37.87±24.726	2372±533	33.67±22.2	<0.001
BMI (kg/m^2)	29.0±1.531	29.573±3.93	29.133±2.145	0.731
Miscarriage	0.23±0.504	0.28±0.575	0.31±0.679	0.893
*Gestational age (weeks)	35.743±3.077	33.895±1.766	35.269±3.018	0.710
[b]AC measurement (weeks)	31.6±3.22	28.7±2.92	35.19±3.3	<0.001
Adiponectin (pg/mL)	94.041±68.254	55.717±23.915	51.831±43.643	0.004
AFI (cm)	39.3±18.4	52.1±24.6	108.6±53.2	<0.001
Weight Gain (kg)	9.19±4.53	10.2±2.6	12.23±6.34	0.017

BMI: body mass index; AC: abdominal circumference; AFI: amniotic fluid index; IUGR: intrauterine growth retardation
*: calculated according to the last menstruation period or first trimester ultrasonography
[b]: the median of the ultrasonography measurement of abdominal circumference, $p<0.05$ is significant.
Values are given as mean±SD.

The mean concentrations of adiponectin were 94.041 pg/mL in the IUGR group, 55.717 pg/mL in the IUGRcwPE group, and 51.831 pg/mL in the control group (Figure 1). The level of adiponectin concentrations was significantly higher in women with IUGR than in the IUGRcwPE and control groups ($p<0.05$ and $p<0.001$, respectively). However, there were no significant differences among the IUGRcwPE and control groups ($p>0.05$). There was no statistically significant correlation between the serum maternal adiponectin levels and age, BMI, and gestational age (Table 2).

Discussion

In the current study, we analyzed the prognostic role of maternal serum adiponectin concentrations in IUGR and IUGRcwPE.

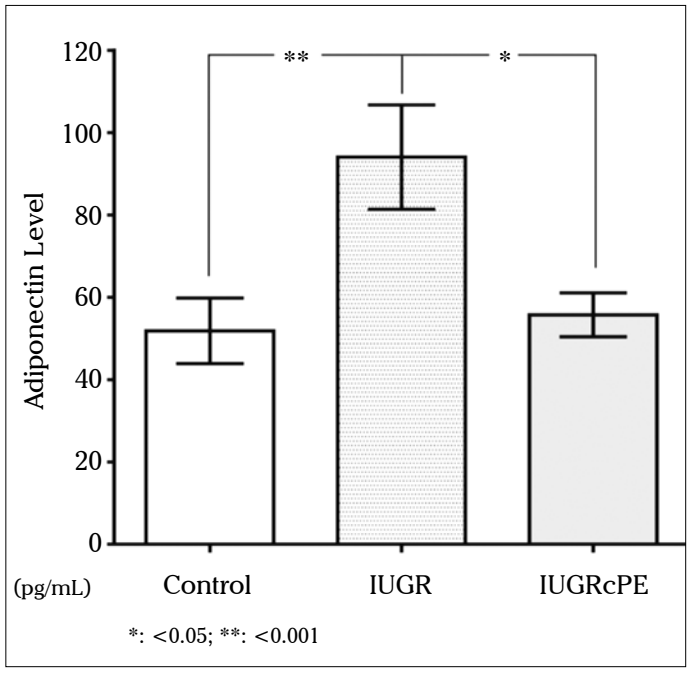

Figure 1. The adiponectin concentrations of the groups

Table 2. Correlation between serum maternal adiponectin levels and clinical parameters

	Age		BMI		Gestational Age	
	r	p	r	p	r	p
Adiponectin	-0.104	0.713	0.072	0.799	0.342	0.728

R: Pearson correlation coefficient; BMI: body mass index
p<0.05 is significant.

A total of 80 pregnant women were included into the study; of all women, 30 (37.5%) were in the IUGR group, 20 (25%) were in the IUGRcwPE group, and 30 (37.5%) were in the control group. We found that adiponectin concentrations were statistically significantly higher in the IUGR group when compared with the IUGRcwPE and control groups.

Adiponectin is a substance that is produced in adipose tissue and released into the bloodstream and has angiogenic, atherosclerotic, insulin-sensitizing, and anti-inflammatory properties (19). In the absence of adiponectin, impaired trophoblastic invasion, endothelial damage, increased insulin resistance, and increased atherosclerosis may present, as seen in pre-eclampsia (19). Contrary to our study, Ramsay et al. (20) showed an increase in adiponectin concentrations in pre-eclamptic women. In two other studies designed by Naruse et al. (19) and Lu et al. (21), adiponectin concentrations were found to be higher in pre-eclamptic pregnant women than normotensive pregnant women. They suggested that endothelial damage may cause elevated adiponectin concentrations. Jarvenpaa et al. (22) studied the adiponectin and adiponectin receptor genes from placental tissue from pre-eclamptic women by polymerase chain reaction (PCR) method and observed a decrease in adiponectin and adiponectin receptor genes and an increase in apoptosis. An association between low adiponectin concentrations and pre-eclampsia was shown in another study, and the researchers suggested that low adiponectin concentrations may be a predictive marker of the etiopathogenesis of pre-eclampsia (23). In our study, we found similar serum maternal adiponectin concentrations in the IUGRcwPE and control groups.

Some studies (24, 25) reported a positive correlation between IUGR and elevated serum maternal adiponectin concentrations, similar to our study. Fasshauer et al. (26) reported an association between impaired uterine perfusion and increased serum maternal adiponectin concentrations due to endothelial damage. On the other hand, Savvidou et al. (27) reported no association between serum maternal adiponectin concentrations in the middle trimester in women who had IUGR. In a study, adiponectin and leptin concentrations were studied from maternal blood before delivery in umbilical cords in women with IUGR, and it found a decline in adiponectin concentrations and revealed this condition with chronic stress, as in IUGR pathogenesis (16). Street et al. (28) found lower adiponectin concentrations in umbilical cord blood samples in IUGR when compared with a control group and commented that the decline was suppression of adiponectin synthase by chronic inflammation. A recent study by Valdes et al. (29) reported that maternal serum adiponectin concentrations were not useful in predicting subsequent development of IUGR; however, maternal adiponectin concentrations were higher in pregnant women during the first trimester who developed IUGR later. In our study, we found higher maternal adiponectin concentrations in the isolated IUGR group when compared with the IUGRcwPE and control groups.

In conclusion, we detected high maternal serum adiponectin concentrations in isolated IUGR and unchanged adiponectin concentrations in IUGRcwPE. This situation may be explained by the compensatory protective effect of adiponectin in pregnancy with IUGR, and we think that this compensatory mechanism has become insufficient when pre-eclampsia occurs. Further studies that involve more participants are required to understand the role of adiponectin in IUGR and IUGRcwPE.

Ethics Committee Approval: *Ethics committee approval was received for this study from the ethics committee of Zekai Tahir Burak Education and Research Hospital.*

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

Peer-review: *Externally peer-reviewed.*

Author contributions: *Concept - B.B., N.D.; Design - B.B., H.O.T.; Supervision - Y.E-Ü., N.D.; Resource - B.B., H.O.T.; Materials - B.B., H.O.T.; Data Collection&/or Processing - B.B., H.O.T.; Analysis&/or Interpretation - B.B., H.O.T., Y.E-Ü. ; Literature Search - B.B., H.O.T., Y.E-Ü.; Writing - H.O.T, B.B.; Critical Reviews - Y.E-Ü., N.D.*

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

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

References

1. Maeda K, Okubo K, Shimomura I, Funahashi T, Matsuzawa Y, Matsubara K. cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (AdiPose Most abundant Gene transcript 1). Biochem Biophys Res Commun 1996; 221: 286-9. [CrossRef]
2. Ouchi N, Kihara S, Arita Y, Maeda K, Kuriyama H, Okamoto Y, et al. Novel modulator for endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. Circulation 1999; 100: 2473-6. [CrossRef]
3. Arita Y, Kihara S, Ouchi N, Maeda K, Kuriyama H, Okamoto Y, et al. Adipocyte-derived plasma protein adiponectin acts as a platelet-derived growth factor-BB-binding protein and regulates growth factor-induced common postreceptor signal in vascular smooth muscle cell. Circulation 2002; 105: 2893-8. [CrossRef]
4. Hotta K, Funahashi T, Bodkin NL, Ortmeyer HK, Arita Y, Hansen BC, Matsuzawa Y. Circulating concentrations of the adipocyte protein adiponectin are decreased in parallel with reduced insulin sensitivity during the progression to type 2 diabetes in rhesus monkeys. Diabetes 2001; 50: 1126-33. [CrossRef]
5. Yang WS, Lee WJ, Funahashi T, Tanaka S, Matsuzawa Y, Chao CL, et al. Weight reduction increases plasma levels of an adipose-derived anti-inflammatory protein, adiponectin. J Clin Endocrinol Metab 2001; 86: 3815-9. [CrossRef]
6. Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, et al. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med 2001; 7: 941-6. [CrossRef]
7. Anonymous. Intrauterine growth retardation. Clinical Management Guidelines for Obstetrician-Gynecologists. ACOG Pract Bull 2000: 1-11.
8. Sibai BM, Caritis S, Hauth J, National Institute of Child H, Human Development Maternal-Fetal Medicine Units N. What we have learned about preeclampsia. Semin Perinatol 2003; 27: 239-46. [CrossRef]
9. Chen J, Tan B, Karteris E, Zervou S, Digby J, Hillhouse EW, et al. Secretion of adiponectin by human placenta: differential modulation of adiponectin and its receptors by cytokines. Diabetologia 2006; 49: 1292-302. [CrossRef]
10. Cortelazzi D, Corbetta S, Ronzoni S, Pelle F, Marconi A, Cozzi V, et al. Maternal and foetal resistin and adiponectin concentrations in normal and complicated pregnancies. Clin Endocrinol (Oxf) 2007; 66: 447-53. [CrossRef]
11. Mazaki-Tovi S, Kanety H, Pariente C, Hemi R, Wiser A, Schiff E, et al. Maternal serum adiponectin levels during human pregnancy. J Perinatol 2007; 27: 77-81. [CrossRef]
12. Mastorakos G, Valsamakis G, Papatheodorou DC, Barlas I, Margeli A, Boutsiadis A, et al. The role of adipocytokines in insulin resistance in normal pregnancy: visfatin concentrations in early pregnancy predict insulin sensitivity. Clin Chem 2007; 53: 1477-83. [CrossRef]
13. Soylemez N, Demirbag R, Sezen Y, Yildiz A, Akpinar O. [The levels of the leptin and adiponectin according to body mass index and their relationship with oxidative parameters]. Anadolu Kardiyol Derg 2010; 10: 391-6. [CrossRef]
14. O'Sullivan AJ, Kriketos AD, Martin A, Brown MA. Serum adiponectin levels in normal and hypertensive pregnancy. Hypertens Pregnancy 2006; 25: 193-203. [CrossRef]
15. Catalano PM, Hoegh M, Minium J, Huston-Presley L, Bernard S, Kalhan S, et al. Adiponectin in human pregnancy: Implications for regulation of glucose and lipid metabolism. Diabetologia 2006; 49: 1677-85. [CrossRef]
16. Kyriakakou M, Malamitsi-Puchner A, Militsi H, Boutsikou T, Margeli A, Hassiakos D, et al. Leptin and adiponectin concentrations in intrauterine growth restricted and appropriate for gestational age fetuses, neonates, and their mothers. Eur J Endocrinol 2008; 158: 343-8. [CrossRef]
17. Ouyang Y, Chen H, Chen H. Reduced plasma adiponectin and elevated leptin in pre-eclampsia. Int J Gynaecol Obstet 2007; 98: 110-4. [CrossRef]
18. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements--a prospective study. Am J Obstet Gynecol 1985; 151: 333-7. [CrossRef]
19. Naruse K, Yamasaki M, Umekage H, Sado T, Sakamoto Y, Morikawa H. Peripheral blood concentrations of adiponectin, an adipocyte-specific plasma protein, in normal pregnancy and preeclampsia. J Reprod Immunol 2005; 65: 65-75. [CrossRef]
20. Ramsay JE, Jamieson N, Greer IA, Sattar N. Paradoxical elevation in adiponectin concentrations in women with preeclampsia. Hypertension 2003; 42: 891-4. [CrossRef]
21. Lu D, Yang X, Wu Y, Wang H, Huang H, Dong M. Serum adiponectin, leptin and soluble leptin receptor in pre-eclampsia. Int J Gynaecol Obstet 2006; 95: 121-6. [CrossRef]
22. Jarvenpaa J, Vuoristo JT, Santaniemi M, Ukkola O, Savolainen ER, Jaaskelainen M, et al. Adiponectin induced placental cell apoptosis could be mediated via the ADIPOR1-receptor in pre-eclampsia with IUGR. J Perinat Med 2009; 37: 257-62. [CrossRef]
23. D'Anna R, Baviera G, Corrado F, Giordano D, Di Benedetto A, Jasonni VM. Plasma adiponectin concentration in early pregnancy and subsequent risk of hypertensive disorders. Obstet Gynecol 2005; 106: 340-4. [CrossRef]
24. Evagelidou EN, Giapros VI, Challa AS, Kiortsis DN, Tsatsoulis AA, Andronikou SK. Serum adiponectin levels, insulin resistance, and lipid profile in children born small for gestational age are affected by the severity of growth retardation at birth. Eur J Endocrinol 2007; 156: 271-7. [CrossRef]
25. Suliman SG, Stanik J, McCulloch LJ, Wilson N, Edghill EL, Misovicova N, et al. Severe insulin resistance and intrauterine growth deficiency associated with haploinsufficiency for INSR and CHN2: new insights into synergistic pathways involved in growth and metabolism. Diabetes 2009; 58: 2954-61. [CrossRef]
26. Fasshauer M, Bluher M, Stumvoll M, Tonessen P, Faber R, Stepan H. Differential regulation of visfatin and adiponectin in pregnancies with normal and abnormal placental function. Clin Endocrinol (Oxf) 2007; 66: 434-9. [CrossRef]
27. Savvidou MD, Sotiriadis A, Kaihura C, Nicolaides KH, Sattar N. Circulating levels of adiponectin and leptin at 23-25 weeks of pregnancy in women with impaired placentation and in those with established fetal growth restriction. Clin Sci (Lond) 2008; 115: 219-24. [CrossRef]
28. Street ME, Volta C, Ziveri MA, Viani I, Bernasconi S. Markers of insulin sensitivity in placentas and cord serum of intrauterine growth-restricted newborns. Clin Endocrinol (Oxf) 2009; 71: 394-9. [CrossRef]
29. Valdes ER, Lattes KA, Munoz HS, Barja PY, Papapietro KV. First-trimester adiponectin and subsequent development of preeclampsia or fetal growth restriction. Gynecol Obstet Invest 2011; 72: 152-6. [CrossRef]

This article will be credited by TMA within the scope of CME/CPD.

Ovarian cystectomy in endometriomas: Combined approach

Cihat Ünlü[1], Gazi Yıldırım[2]

[1]Department of Obstetrics and Gynecology, Acıbadem University, Bakırköy Acıbadem Hospital, İstanbul, Turkey

[2]Department of Obstetrics and Gynecology, Yeditepe University Hospital, İstanbul, Turkey

Abstract

Endometrioma is one of the most frequent adnexal masses in the premenopausal population, but the recommended treatment is still a subject of debate. Medical therapy is inefficient and can not be recommended in the management of ovarian endometriomas. The general consensus is that ovarian endometriomas larger than 4 cm should be removed, both to reduce pain and to improve spontaneous conception rates. The removal of ovarian endometriomas can be difficult, as the capsule is often densely adherent. While the surgical treatment of choice is surgical laparoscopy, for conservative treatment, the preferred method is modified combined cystectomy. Cystectomy can be destructive for the ovary, whereas ablation may be incomplete, with a greater risk of recurrence. To the best of our knowledge, the modified combined technique seems to be more efficient in the treatment of endometriomas. (J Turk Ger Gynecol Assoc 2014; 15: 177-89)

Key words: Endometrioma, laparoscopy, cystectomy, combined technique

Received: 25 August, 2014 **Accepted:** 29 August, 2014

Introduction

The ovaries are a common site for endometriosis. Endometrioma is one of the most frequent adnexal masses in the premenopausal population (Figure 1). Although endometrioma is the most frequent ovarian mass that is encountered by gynecologists, there are still controversies on its pathogenesis, risk of malignant transformation, modalities of treatment, and effect on fertility.

Laparoscopy is extremely useful in the diagnosis and treatment of endometriomas. The purpose of this chapter is to highlight the steps and tips of the surgical removal of endometriomas by combined approach.

Diagnosis

The definitive diagnosis of the endometriosis is made by visualizing lesions during surgery and obtaining histological confirmation. Transvaginal sonography has been found to be a good test for assessing the severity of pelvic endometriosis. The morphology of ovarian endometriomas in the ultrasonography examination reveals a round, homogenous, hypoechoic cyst with or without internal septa and with poor vascularization of the cyst wall. Diffuse low-level internal echoes occur in 95% of endometriomas. Endometriomas are usually adherent to the pelvic side wall. This immobility is a useful diagnostic indicator. Levels of serum and other concentrations of hormones may eventually be categorized, such that they provide prognostic and/or treatment capabilities for patients with endometriomas. Lower anti-mullerian hormone serum levels and an association with the severity were found in women with endometriosis. This information might be useful in patients, especially those with severe endometriosis undergoing controlled ovarian stimulation (1). Putative serum markers (monocyte chemoattractant protein 1, migration inhibitory factor, leptin, and CA-125) improved their diagnostic capability to 73% of patients, with 94% overall accuracy (2).

A new marker, HE4 (human epididymis secretory protein-4), could be used in the differential diagnosis of endometriosis cyst. Human epididymal secretory protein E4 is a new promising biomarker for ovarian cancer. The combination of HE4 and CA 125 assay could discriminate ovarian endometriosis cysts from malignant ovarian tumors effectively (3). The advantage of HE4 over CA125 is mainly in the detection of borderline ovarian tumors and early-stage epithelial ovarian and tubal cancers (4). A normal HE4 value in this situation would imply the differential diagnosis of a benign endometrioma rather than ovarian cancer, and this patient could therefore be operated on laparoscopically by a gynecologist. Both markers showed similar diagnostic performance in the detection of epithelial ovarian cancer at clinically defined thresholds (CA125 35 U/mL; HE4 70 pM), but HE4 was not elevated in endometriosis (5). An analysis of serum HE4 concentrations together with a tumor marker, CA125, in serum samples of women diagnosed with various types of endometriosis, endometrial cancer, or ovarian cancer and in samples from healthy controls has been released (6). Based on this study, the mean serum concentration of HE4 was significantly

Address for Correspondence: *Cihat Ünlü, Department of Obstetrics and Gynecology, Acıbadem University, Bakırköy Acıbadem Hospital, İstanbul, Turkey. Phone: +90 212 241 45 45 e.mail: mcihatunlu@gmail.com*

DOI:10.5152/jtgga.2014.1111

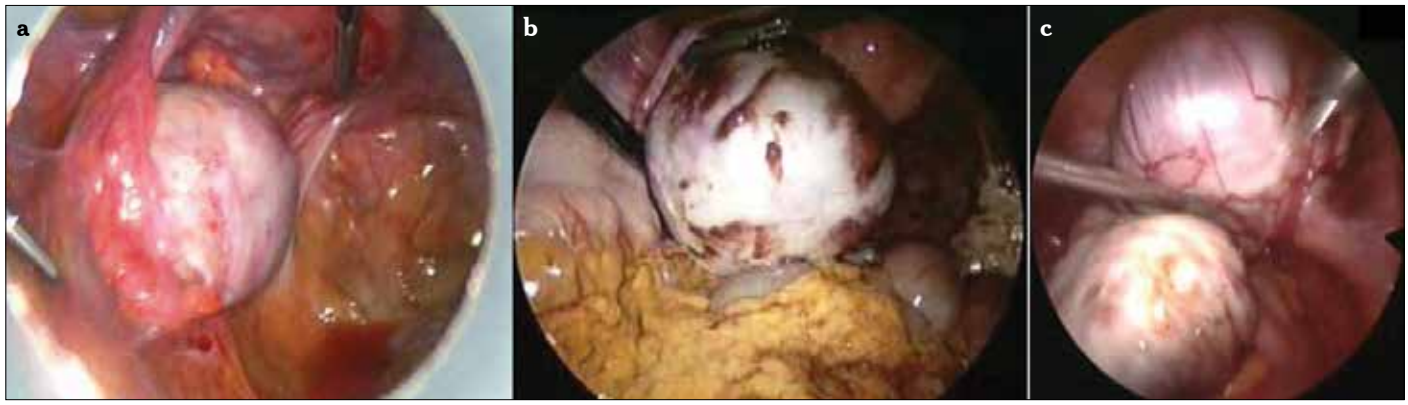

Figure 1. a-c. Ovarian endometriomas. Small endometrioma (a), large endometrioma and ovarian implants of endometriosis (b), bilateral endometrioma, kissing ovaries (c)

higher in serum samples of patients with both endometrial (99.2 pM, $p<0.001$) and ovarian (1125.4 pM, $p<0.001$) cancer but not with ovarian endometriomas (46.0 pM) or other types of endometriosis (45.5 pM) as compared with healthy controls (40.5 pM). Serum CA125 concentrations were elevated in patients with ovarian cancer, advanced endometriosis with peritoneal or deep lesions, or ovarian endometriomas. Taken together, it can be postulated that measuring both HE4 and CA125 serum concentrations increases the accuracy of ovarian cancer diagnosis and provides valuable information to discriminate ovarian tumors from ovarian endometriotic cysts. Serum HE4 concentration is a valuable marker to better distinguish patients with ovarian malignancies from those suffering from benign ovarian endometriotic cysts.

However, the different diagnostic modalities that have been discussed demonstrate that there are many candidates but no good non-invasive tests to replace laparoscopic visualization for diagnosis and staging, preferably with histologic confirmation. Laparoscopy has the advantage of allowing simultaneous diagnosis, staging, and treatment of ovarian endometriosis.

Laparoscopy for Endometriomas

Indications for Surgery

Five specific complications may be associated with the non-surgical approach: 1) risk of causing rupture of the endometrioma and/or the development of a pelvic abscess, 2) missing an occult early-stage malignancy, 3) difficulties during oocyte retrieval, 4) follicular fluid contamination with endometrioma content, and 5) progression of endometriosis (7).

Endometriosis is shown to increase the risk of certain subtypes of ovarian cancer, such as endometrioid and clear-cell carcinomas (8). There are data indicating that 40% of endometrioid ovarian carcinomas and 50% of clear-cell ovarian carcinomas are associated with endometriosis. Both endometrioid and clear-cell carcinomas are thought to arise, at least partly, from endometriosis. Similar pathophysiological mechanisms may be involved in the progression of endometriosis, as well as in its transformation into ovarian neoplasia (9). Expectant management without a tissue diagnosis does not exclude the possibility of malignancy, particularly in older woman.

Table 1. Surgical decision for the endometriomas before IVF treatment

	Favors surgery	**Favors expectant management**
Previous interventions for endometriosis	None	≥1
Ovarian reserve	Intact	Damaged
Pain symptoms	Present	Absent
Location	Unilateral disease	Bilateral disease
Sonographic feature of malignancy	Present	Absent
Growth	Rapid growth	Stable
IVF: *in vitro* fertilization		

The recommended treatment is still a subject of debate. Management of endometrioma before *in vitro* fertilization (IVF) remains controversial. The clinical variables to be considered when deciding whether to perform surgery or not in women with endometriomas selected for IVF are listed in Table 1 (modified from reference 10). However, medical treatment for the endometrioma does not improve fertility. Surgical treatment is effective in the treatment of pain and fertility, particularly for women with more severe endometriosis. It improves pelvic pain and deep dyspareunia. Draining the endometrioma or partially resecting its wall is inadequate, because the endometrial tissue lining the cyst can remain functional and may cause the symptoms to recur. Cystectomy of ovarian endometriomas improves spontaneous pregnancy rates and reduces pain. In addition, it may improve the response to *in vitro* fertilization (IVF). It has been shown that laparoscopic cystectomy for ovarian endometriomas >4 cm in diameter improves fertility compared to drainage and coagulation (11). Drawbacks of surgery include postoperative adhesion formation and incomplete removal of the disease. Laparoscopy has the advantage of allowing simultaneous diagnosis, staging, and treatment of ovarian endometriosis. The main surgical procedures for treatment of endometrioma include ultrasound-guided or laparoscopy-guided aspiration, laparoscopic surgery by means of cystectomy or fenestration and coagula-

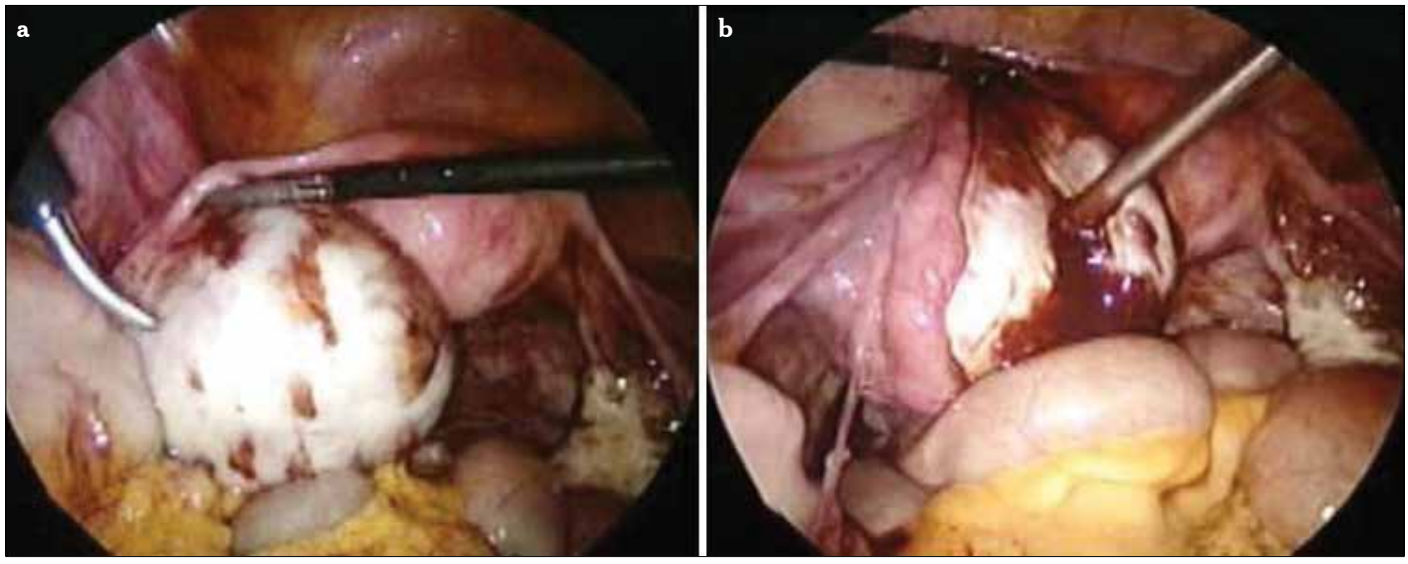

Figure 2. a, b. Laparoscopic aspiration of the endometrioma cyst. Hemosiderin staining on the ovary clued about endometrioma (a), aspiration (b)

Table 2. Surgical procedures for the endometriomas

Conservative treatment
• Transvaginal Ultrasonography-Guided Aspiration (TUGA)
• Laparoscopic Aspiration
• Fenestration and Ablation (Fulguration or Vaporization)
• Total Cystectomy
• Cystectomy with Combined Technique
Radical treatment
• Salpingo-Oophorectomy
TUGA: Transvaginal Ultrasonography-Guided Aspiration

tion, radical-treatment ovariectomy or adnexectomy, and treatment by laparotomy (Table 2 (modified from reference 12)).

Surgical Technique

A general consensus is that ovarian endometriomas larger than 4 cm should be removed, both to reduce pain and to improve spontaneous conception rates. The presence of small endometriomas (2-4 cm) does not reduce the success of *in vitro* fertilization (IVF) treatment (13). However, all decisions to operate a cyst beyond 3 or 4 cm are arbitrary, as there is no evidence to support one or the other (10). Surgeons should bear in mind that if all healthy growing follicles may be reached without damaging the endometrioma, a cyst over 4 or even 5 cm does not require surgery in asymptomatic patients; however, smaller cysts that hide growing follicles, especially when the ovary is fixed, may require intervention.

The goal of operative treatment of endometriosis is to remove all implants, resect adhesions, relieve pain, reduce the risk of recurrence and postoperative adhesions, and restore the involved organs to a normal anatomic and physiologic condition. This goal may be achieved by using various surgical instruments (scissors, harmonic scalpel, lasers…) and a variety of techniques (laparoscopy, laparotomy, combined endoscopy, and mini-laparotomy). But, to the best of our knowledge, endometriomas must be treated by laparoscopy. Laparoscopic cystectomy remains a first-line choice for the conservative treatment of endometriotic cysts.

Laparoscopy for endometrioma is performed through an intra-umbilical incision and two or three lower abdominal incisions. Usually, 5-mm bipolar and unipolar scissors and graspers with suction-irrigation systems are enough to complete the surgical procedure. Irrigation is performed by lactated Ringer's solution. Hemostasis is achieved with bipolar coagulation, laser ablation, or new commercially available hemostatic sealant agents.

The procedure begins with laparoscopic inspection of the pelvic anatomy and systemic mapping of the endometriotic lesions. Inspection of the pelvis should be carried out in a logical and systematic way. The liver and diaphragms are inspected to look for endometriotic implants or perihepatic adhesions. Inspect the utero-vesical fold, and lift the uterus forward into anteversion. Move the bowel out of the pouch of Douglas. Fluid in the pouch should be aspirated to ensure that implants are not missed. Inspect both tubes and ovaries. Deep, infiltrating endometriotic implants are often palpated and then visualized. This can be done with a blunt probe or graspers through the second port. Laparoscopy for endometrioma, like surgery for adnexal masses, is started with peritoneal washing for cytology and inspection of the pelvis and intra-abdominal viscera for any type of lesion, like implants or adhesions.

After inspection of the intra-abdominal area and obtaining peritoneal washing, the first step of the surgery is mobilization of the ovaries. The utero-ovarian ligament is taken with a 5-mm atraumatic grasper. Lysis of the adhesions is performed with the use of sharp dissection to fully mobilize the ovaries. Adhesiolysis may be performed using hydrodissection, scissors, CO_2 laser, or atraumatic forceps. Before cutting the handling tissue, it is important to mobilize and identify the relevant anatomical structures. Mechanical dissection with forceps and hydrodissection is not associated with any thermal effect; therefore, this technique should be preferred. The removal of ovarian endometriomas can be difficult, as the capsule is often

densely adherent. Large endometriomas are typically adherent to the back of the uterus or broad ligament or ovarian fossa. Adhesiolysis often results in opening of the cyst and leaking of the 'chocolate' content (Figure 2). In most cases, the cyst is ruptured during mobilization of the ovary, which requires the liquid to be aspirated immediately to prevent pelvic contamination.
Meticulous suction and irrigation are performed to remove this spillage. The perception is that copious irrigation and suction of released endometrioma content reduce adhesion formation; however, there is a lack of clinical literature to evaluate this supposition. An interesting animal study has shown human endometrioma fluid exposure in the peritoneal cavity of rabbits is not associated with adhesion formation. In this study, instillation of endometrioma fluid, followed by copious saline lavage, is strongly associated with adhesion formation (14). A possible explanation for the higher mean clinical adhesion scores in the lavage group is that the saline lavage itself served to spread the endometrioma fluid more effectively in the abdominal cavity, thereby increasing the distribution of tissue contact and potential for adhesions compared to local spillage. Another possibility is that the process of lavage mechanically irritates the peritoneal cavity and thereby causes adhesions by local tissue damage by the suction instrument. There is some evidence that peritoneal irrigation with lactated Ringer's solution is superior to irrigation with normal saline and that lactated Ringer's solution irrigation is protective against adhesions in both rat and rabbit models.
After freeing the ovary, an incision is made to the ovarian cortex with either scissors or a monopolar hook device. CO_2 laser can be used for this purpose. The incision should be in the free surface of the ovary and, when it is possible, on the anti-mesenteric surface and the most distant possible port from the fimbria. Then, the cyst cavity is repeatedly irrigated with a suction-irrigation tube. After cleansing the cyst content, the laparoscope is proceeded to inspect inside of the cyst wall to rule out suspicious malignant lesions, such as vegetations, papillary masses, or solid projections.
It has been known that surgical resection of endometriomas, either by laparotomy or laparoscopy, is equally effective in eradicating endometriosis; however, if resection of endometriomas is not sufficiently radical, the risk of recurrence is high.

Fenestration and Ablation (Fulguration or Vaporization)
Endometrial implants or endometriomas less than 2 cm in diameter are coagulated, laser-ablated, or excised using scissors, biopsy forceps, laser, or electrodes. For successful eradications, all visible lesions and scars must be removed from the ovarian surface. A major problem with laparoscopic cyst drainage is a high risk of recurrence of about 80% to 100% (15). Nowadays, it is accepted that simple aspiration by laparoscopy should not be used to treat endometrioma.
An alternative method is to perform laparoscopic cyst fenestration and ablation of the cyst capsule. Any co-existing endometriosis should also be treated. This has been shown to significantly improve pelvic pain, with a very high patient satisfaction rating. Fenestration and ablation or laser vaporization of endometriomas without excision of the pseudocapsule is associated with a significantly increased risk of cyst recurrence.
Alborzi et al. (16) found that laparoscopic ovarian cystectomy was associated with better outcomes in pregnancy rates and relief of pain than fenestration and coagulation of endometriomas and had a lower rate of reoperation, even in larger cysts. As a result, they recommend that cystectomy of endometriomas is a better option than fenestration and coagulation, especially in patients with infertility and pelvic pain. Laparoscopic stripping of ovarian endometriomas as an intervention to improve fertility is a widespread clinical practice, not only to improve natural fertility but also to improve IVF outcomes. This surgical strategy is used, because older studies suggested that patients with ovarian endometriosis had poorer IVF outcomes than women with other infertility causes, and some data suggest that spontaneous fecundity may improve after laparoscopic cystectomy.
In our practice, we usually do not prefer fenestration, aspiration, and ablation. Laparoscopic cystectomy remains the first-line choice for conservative treatment of endometriotic cysts. But, as it has been told: there is no disease, there is a patient. The treatment should be individualized, based on operative findings and on date conditions.

Total Cystectomy
The surgical technique of ovarian cyst excision by laparoscopy differs from traditional surgery performed by laparotomy. In laparoscopy, most surgeons perform a stripping technique, in which two atraumatic grasping forceps are used to pull the cyst wall and the normal ovarian parenchyma in opposite directions, thus developing the cleavage plane. After excision of the cyst wall, hemostasis is achieved by using bipolar forceps or CO_2 laser. The residual ovarian tissue is not sutured, and the ovarian edges are left to heal by secondary intention. In contrast, in laparotomy, the cleavage plane is developed by using microsurgical techniques and instruments.
After identifying the correct plane (Figure 3), bimanual opposite traction with two -mm grasping forceps (atraumatic one for the handling of the ovarian cortex) is performed to strip the cyst wall from the inner surface of the ovarian tissue (Figure 4). This step is usually difficult compared to functional cyst stripping. When necessary, scissors, bipolar, or laser can be utilized for the stripping step. Another method involves hydrodissection of the plane between the cyst wall and the ovarian stroma (17). The cyst wall is removed by grasping its base with laparoscopic forceps and peeling it from the ovarian stroma. If stripping of the capsule is incomplete or difficult to accomplish, the residual part must be eradicated by electrocoagulation or laser application. During the stripping procedure, meticulous and highly selective coagulation is required.
After removing the cyst wall from the ovary, the bed of the cyst is inspected carefully to visualize the bleeders and to coagulate them with bipolar coagulation (Figure 5), holding the ovary with an atraumatic forceps and visualizing each bleeding site by dripping saline on the base of the cyst. After total stripping, in some cases, annoying bleeding may occur in the bed of the cyst. It should be noted that prompt coagulation can cause diminished ovarian reserve. Especially in this area, monopolar coagulation should be avoided. Careful inspection with a suction and irrigation tube can show the exact point of the bleeders. Only this area should be grasped and coagulated in a low-setting voltage with bipolar forceps.

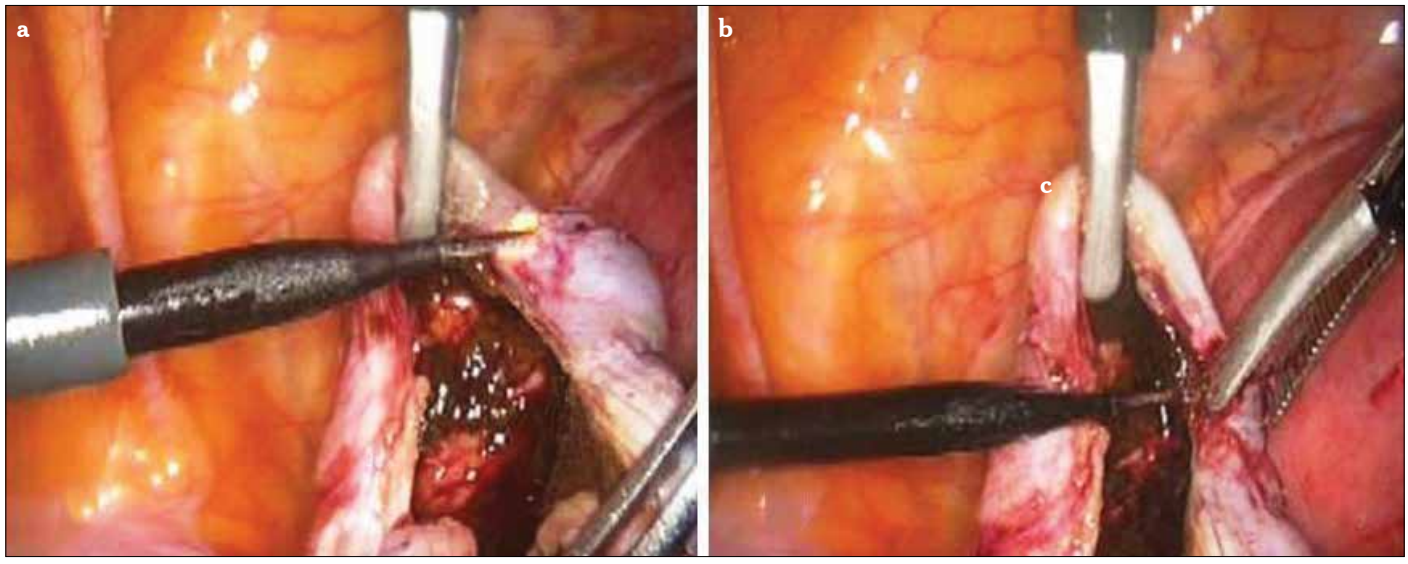

Figure 3. a, b. A needle electrode is used to identify and create a correct cleavage plane between the cyst wall and ovarian cortex

Canis et al. (18) and Marconi et al. (19) found no effect on ovarian response in IVF after cystectomy. But, there are many other trials that indicate that cystectomy has a bad influence in the subsequent ovarian responsiveness. As Hart et al. concluded, excisional surgery of endometriomas results in a more favorable outcome than drainage and ablation in terms of recurrence, pain symptoms, subsequent spontaneous pregnancy in previously subfertile women, and ovarian response to stimulation (20). But, Muzii et al. (21) showed that recognizable ovarian tissue was inadvertently excised together with the endometriotic cyst wall in most cases during stripping for endometrioma excision. Close to the ovarian hilus, ovarian tissue that was removed along the endometrioma wall contained primordial, primary, and secondary follicles in 69% of cases. Away from the hilus, no follicles or only primordial follicles were found in 60% of specimens. There is obviously an absence of a clear plane of cleavage close to the ovarian hilus. However, it has been published by the same group that the ovarian tissue adjacent to the endometrioma wall differs morphologically from normal ovarian tissue; it never shows the follicular pattern that is observed in normal ovaries (22).

In experienced hands, laparoscopic stripping of endometriomas appears to be a technique that does not significantly damage the ovarian tissue. On the contrary, several studies have demonstrated a reduced follicular response after total cystectomy. Nargund et al. showed that, in cycles with ovulation induction after cystectomy, revealed less follicular count in the ovary that underwent surgical excision (23). Ho et al. concluded that surgery for ovarian endometriomas induces a poor ovarian response to controlled ovarian hyperstimulation (24). Laparoscopic cystectomy has been questioned with respect to damage to the operated ovary.

Because of these negative effects, a new technique is required to remove endometrioma without damage to the ovarian tissue with a low subsequent recurrence rate. A modified combined technique for the removal of endometrioma seems to achieve this issue.

Modified Combined Technique vs Total Cystectomy

Preservation of the vascular blood supply to the ovary is important. A proper blood supply is vital for the preservation of ovarian volume and antral follicular counts. Meticulous surgical techniques avoiding the compromise of ovarian blood supply and healthy ovarian tissue are mandatory, but still, it can be postulated that there are two main risks associated with the surgical treatment of endometriomas: the risk of excessive surgery (removal or destruction of normal ovarian cortex together with the endometrioma) and the risk of incomplete surgery (with subsequent early recurrence of endometriomas) (25). To overcome these problems, Donnez et al. described a new mixed technique for the laparoscopic management of endometriomas (26). They defined their technique as follows. The endometrial cyst is opened and washed out with irrigation fluid. After identifying the plane of cleavage between the cyst wall and ovarian tissue by applying opposite bimanual traction and counter-traction with two grasping forceps, providing strong but nontraumatic force, the inner lining of the cyst is stripped from the normal ovarian tissue. If the excision provokes bleeding or if the plane of cleavage is not clearly visible, the cystectomy is stopped because of the risk of removing normal ovarian tissue containing primordial, primary, and secondary follicles along with the endometrioma. They claimed that when approaching the hilus, where the ovarian tissue is more functional and the plane of cleavage is less visible, resection of the dissected tissue (partial cystectomy) is performed. Then, after this first step (partial cystectomy), CO2 laser is used to vaporize the remaining 10%-20% of the endometrioma close to the hilus. They do not close the ovary after the operation.

Based on these sights, we developed our modified combined technique (Figure 6). In this technique, after initial inspection and peritoneal cytology, obtained with washing of the peritoneal cavity, adhesiolysis is performed. The ovary is released from the attachments, and pelvic anatomical restoration is obtained. The endometrial cyst is opened with a fine-tip electrode with a low power setting (30 watts). The cyst content is irrigated and

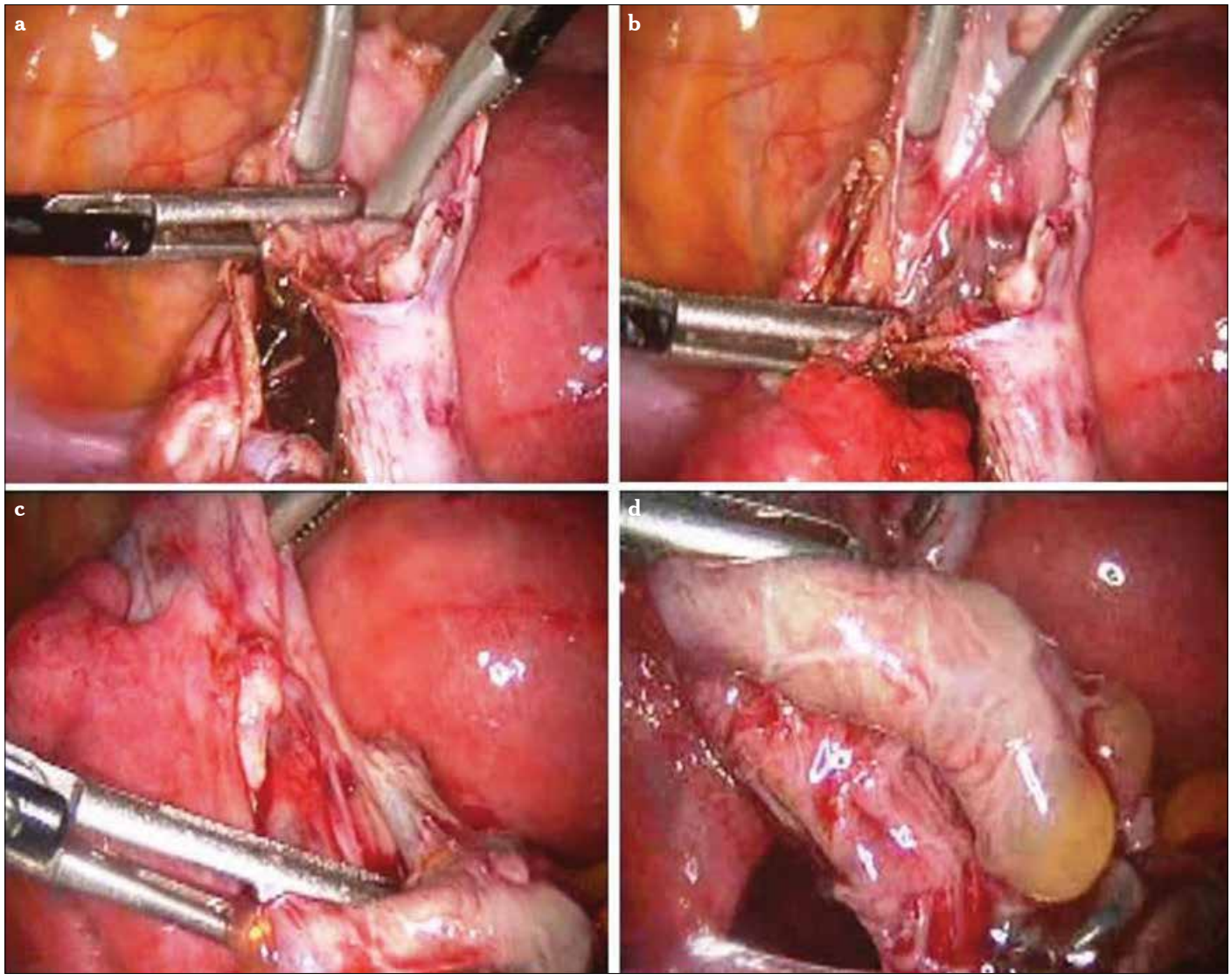

Figure 4. a-d. Cyst wall grasped with either traumatic or atraumatic forceps and ovarian cortex handled all the time with the atraumatic one. Countertraction for the stripping (a-c). Total cystectomy (d)

aspirated to prevent spillage into the pelvis. The true cleavage plane is found as described earlier.

The cyst wall and the ovarian cortex are grasped, and gentle traction and countertraction are applied for the stripping of the cyst wall from its bed. The traction is ceased when reaching the hilus. This area looks pale due to fibrotic tissue. Forcing the traction can cause bleeding easily in this area. To avoid damage to the ovary, we do not proceed with stripping after this step. Till here, the stripping technique allows removal of 80%-90% of the cyst. Then, the cyst wall is coagulated with bipolar forceps (40 watts) around this area. In contrast to total cystectomy, coagulation of the cyst wall in the combined technique protects the ovarian tissue from heat damage. Then, the coagulated cyst wall is incised, and cystectomy is achieved. Care must be taken to cauterize all of the residual cyst wall to avoid recurrence. The coagulation of the cyst wall prevents small bleeding and protects patients from diminished ovarian reserve. At the end of the procedure, the ovary is not sutured. We know that stretching of the ovarian cortex does not seem to be associated with morphologic alterations. Electrosurgical coagulation of the remaining parenchyma after excision of the cyst wall may cause further damage to the ovarian tissue. However, when appropriate techniques are used, small vessels may be identified and coagulated with bipolar forceps that, under these circumstances, may limit thermal damage to less than 0.2 mm (27). But, there is still a small risk for heat injury. In the combined technique, even if the heat spreads, it still projects onto the capsule (Figure 7). This thermal spreading only prevents recurrence, as it does not proceed from the cyst wall to the ovarian cortex or hilus.

To reduce the probability of ovarian tissue damage, hemostatic agents can be used for the hemostasis of the cyst bed. Fibrin sealant is an excellent agent to use for sealing small bleeders. We generally use the PerClot system (Figure 8). This is a medical device composed of absorbable modified polymer (AMP) particles and delivery applicators. AMP particles are

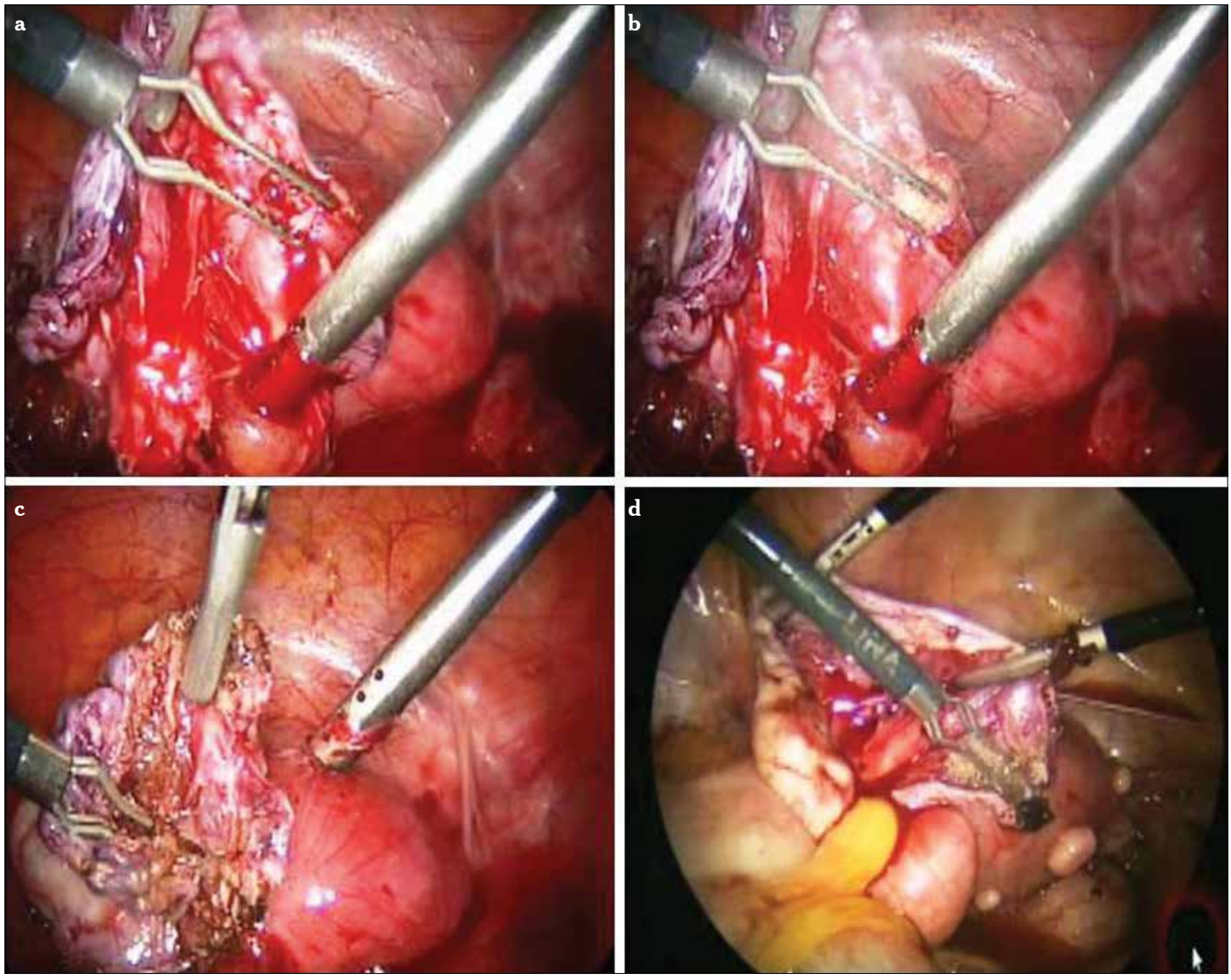

Figure 5. a-d. After total stripping, sometimes meticulous hemostasis is needed. Prompt coagulation can cause diminished ovarian reserve

biocompatible and non-pyrogenic and derived from purified plant starch (SMI-Starch Medical Inc., San Jose, California, USA). Some products, like Tisseel, distributed in the United States by Baxter Healthcare Corp. (Glendale, California, USA); Crosseal (the American Red Cross, OMRIX biopharmaceuticals Ltd., Kiryat Ono, Israel); and FLOSEAL (Baxter's BioScience-Glendale, California, USA) can be used.

The endometriotic cyst wall is removed from a 5 mm trocar if it is small in size (Figure 9). The surgeon draws the tissue into the port sleeve using gentle rotation and opens the flapper valve as the specimen is withdrawn. If there is any suspicion for a malignancy or a great mass that can not be extracted from small-sized trocar, then an endobag can be used (Figure 10). Endobags usually need a 10 mm or 12 mm trocar. There are two options: either to replace one of the ancillary 5 mm ports to the 10 mm trocar or to use a 5 mm telescope. The 5 mm scope is introduced from one of the pelvic ancillary trocars, and the endobag is introduced to the abdomen from the umbilical port. For slightly larger benign specimens, the 10-12 mm umbilical sleeve is often adequate for tissue removal. If the surgeon is not using an operative (10 mm) laparoscope, a 5 mm laparoscope may be introduced through one of the lateral ports, and the tissue is recovered with a grasping forceps under direct vision using either of the techniques above. If there is no 5 mm scope under the hands, then our technique can be applied for tissue retrieval (Figure 11). A traumatic grasper is introduced through the ancillary port, and the scope proceeds from the umbilical port. The grasped tissue follows the tip of the scope, and with gradual pulling back of the scope, the tissue is proceeded to the lumen of the umbilical port. Whenever the scope is taken back from the port, the grasper is promoted in the umbilical port, and the tissue is taken out. Once removed from the abdominal cavity, the cyst has to be sent for histopathological examination.

Intra-abdominal adhesions lead to significant morbidity. Unfortunately, pelvic surgery for endometriosis has been associated with high rates of adhesion formation and reformation (29). After laparoscopic endometriosis surgery, the odds of adhesion formation range from 80% to 100% (30). The high incidence

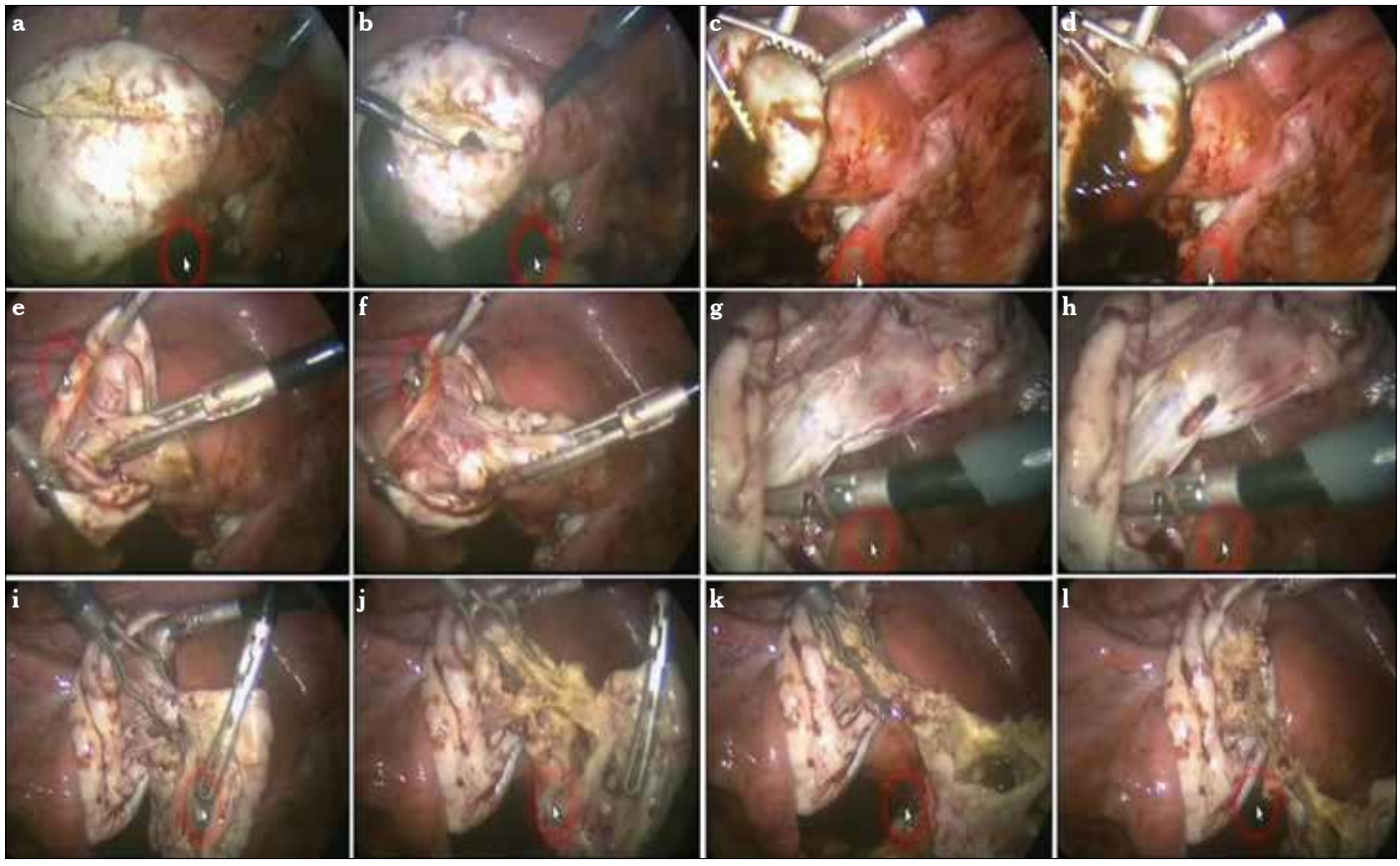

Figure 6. a-l. Modified combined technique for the removal of endometrioma. Cleavage plane is revealed with a fine-tip needle electrode (a, b). Countertraction is accomplished to strip the cyst wall from the ovarian cortex (c-f). When the base of the cyst is reached, a white plane is seen (g). With more traction, the tissue usually starts to tear (h). Cyst wall is coagulated using bipolar forceps and cut from the base with scissors (i-l)

of adhesion formation after surgery for endometriosis underscores the importance of optimizing the surgical technique and the possible role of anti-adhesion drugs to potentially reduce adhesion formation. To reduce postoperative adhesion, we prefer to use adhesion barrier gels (Hyalobarrier Gel; The Nordic Group, Paris France) (Figure 12).

If there is a need for putting a drain in after the surgery, a 14-16 F rubber drain can be applied into the abdomen. A grasper with teeth is introduced from one ancillary trocar to the others. When the tip of the grasper reaches the outside through the second port, this trocar is taken out, and the tip of the end side of the drain is held with this grasper. Then, the grasper is pulled back to introduce the drain into the pouch of Douglas. This is an easy way to put a in rubber drain in any sort of laparoscopic surgery (Figure 13).

Conclusion

Medical therapy is inefficient and can not be recommended in the management of ovarian endometriomas. While the surgical treatment of choice is surgical laparoscopy, for conservative treatment, the preferred method is modified combined cystectomy. There are no indications for systematic pre-operative medical treatment to facilitate the cystectomy. Post-operative medical treatment has no benefits in cases of infertility. But, treatment of the endometriosis, as well as endometriomas, must be individualized, taking the clinical problem in its entirety into account, including the impact of the disease and the effect of its treatment on quality of life. Therefore, it is vital to take careful note of the woman's complaints and to give her time to express her concerns and anxieties, as in other chronic diseases.

The excision of the cyst wall in endometriomas is strongly recommended, especially in infertile patients. However, in light of all of this evidence, we can conclude that cystectomy may be destructive to the ovary. On the contrary, inefficient coagulation may create a great risk of recurrence. The modified combined technique, therefore, is the best approach to remove the endometrioma without increasing the recurrence rate and ovarian tissue damage.

It is essential to minimize or avoid spillage of endometrioma contents during surgical resection and thereby avoid the need for irrigation and suction. Use of careful dissection, aspiration of the endometrioma fluid before rupture, and a sterile bag collection device to avoid spillage of the endometrioma fluid are possible substitute techniques to the currently accepted surgical approach.

It has been shown that the stripping procedure used in laparoscopy for ovarian cyst excision appears to be an organ-preserving procedure. Besides, in non-endometriotic cysts, some

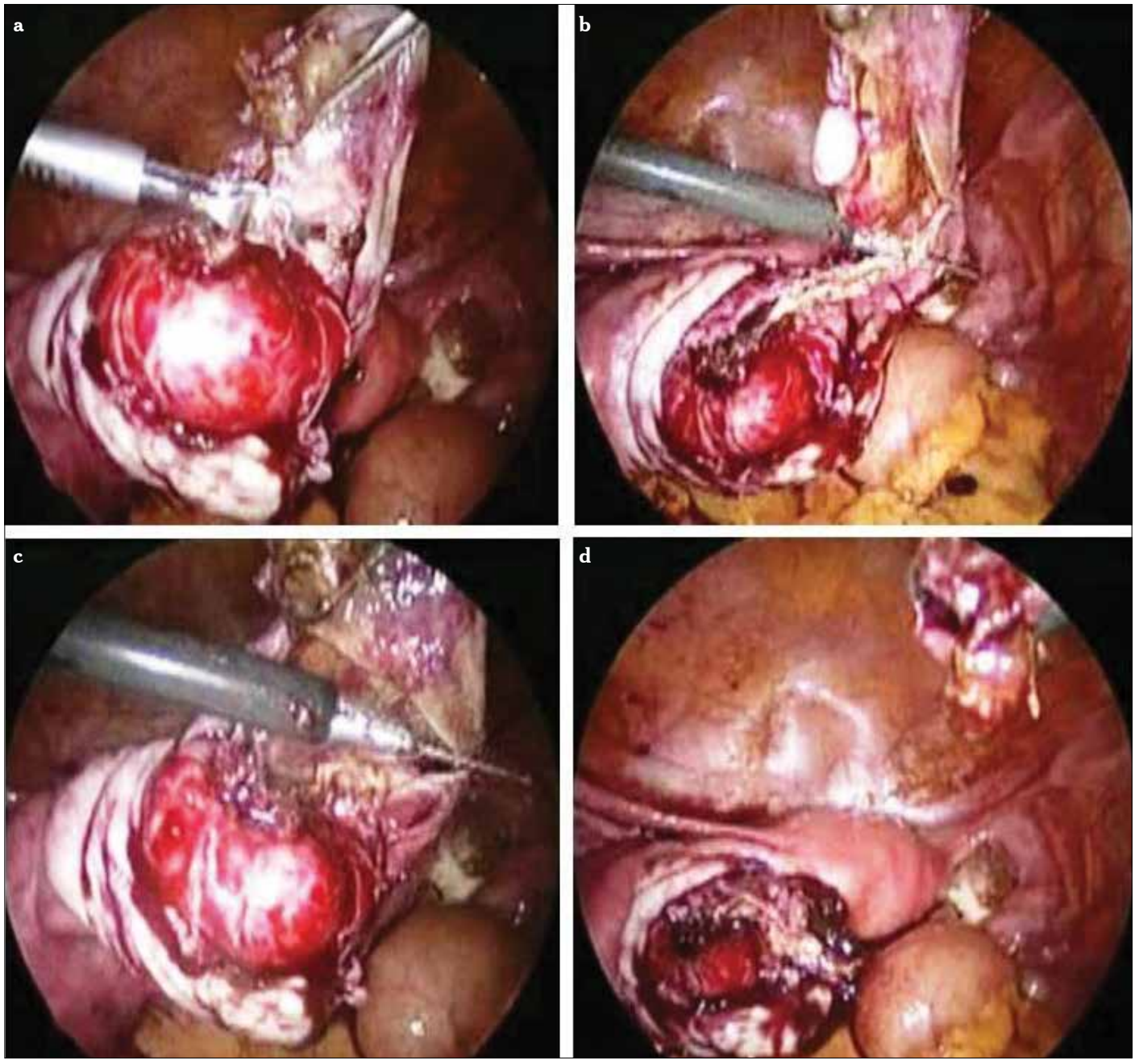

Figure 7. a-d. The ovarian cortex is protected from the side effect of heat when coagulation is applied only to the base of the cyst wall in the modified combined technique

ovarian tissue was inadvertently excised with the cyst wall in the endometriotic cysts. These specimens included some ovarian tissue, approximately 1-2 mm in thickness, excised along with the cyst pseudocapsule; this tissue, however, did not show the morphologic characteristics seen in normal ovarian tissue. Still, it should be kept in mind that there is lack of evidence in long-term follow-up. Therefore, meticulous attention should be given during the stripping procedure.

The learning curve for difficult surgical procedures, such as the adequate treatment of ovarian endometrioma, is probably the most important point. To overcome this problem, surgeons have to attend courses, buy books, and read papers to learn the technique in detail. They have to convince the hospital directors that they should buy a new set of expensive and often fragile instruments and collaborate with the anesthesiologists, who may have to adapt their practice to the requirements of endoscopy. Finally, they have to start the technique and train the operating theater team. As time goes on, their technique will improve, the conversion rate to laparotomy will decrease, and the advantages of laparoscopy will become obvious. There is ample evidence to show that every gynecologic surgeon should move to laparoscopy to manage benign adnexal condi-

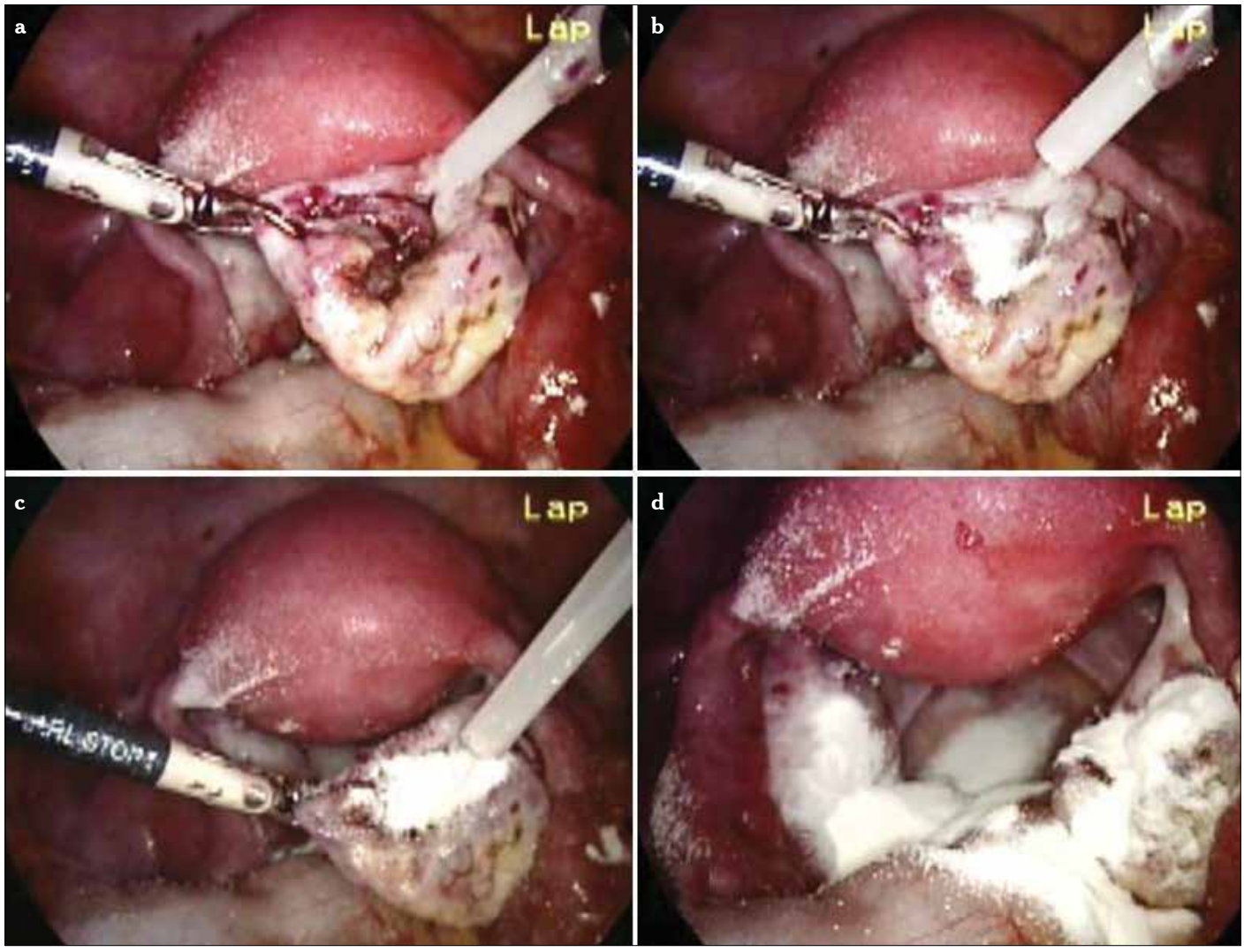

Figure 8. a-d. Hemostatic powders can be used to achieve adequate hemostasis

Figure 9. a-c. Cyst wall is taken out from the ancillary trocar

tions. They should be willing to learn the technique and simply have to accept the stress and the time involved with the development of the endoscopic revolution in their own department. From our experience in teaching laparoscopy to residents, we are convinced that for young surgeons, training for endoscopy is similar to training for laparotomy.

It should be remembered that some recent data add evidence against laparoscopic ovarian surgery for endometriomas in asymptomatic patients who are candidates for IVF. For this purpose, a meticulous surgical technique should be applied to the endometriomas. Laparoscopic ovarian cystectomy is recommended if an ovarian endometrioma ≥4 cm in diameter is

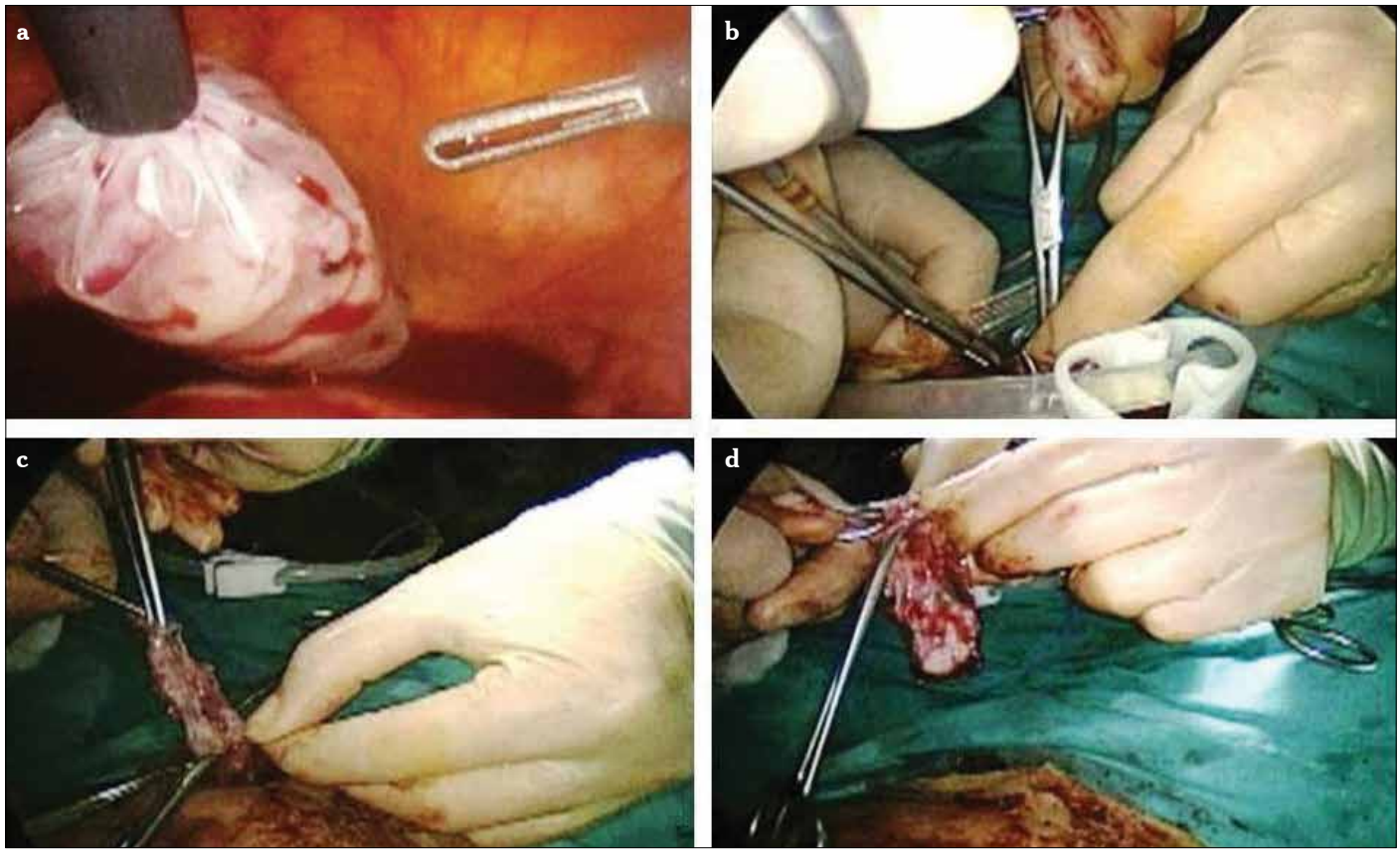

Figure 10. a-d. An endobag can be used for removing the cyst from the abdomen

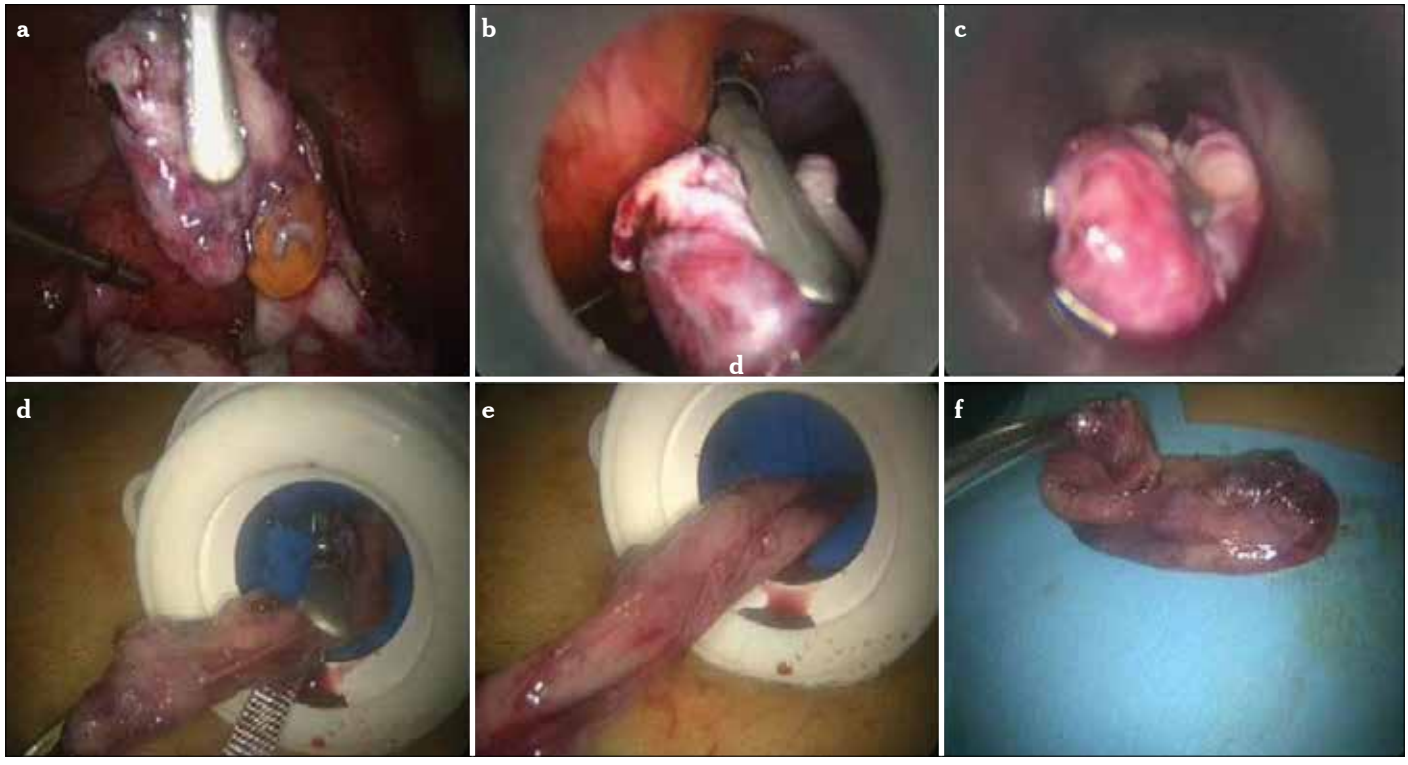

Figure 11. a-f. A big mass can be introduced to the 10-mm scope's trocar. Stripped endometrioma cyst wall is grasped (a). The grasped tissue is proceeded toward the scope, and gradually, the scope is pulled back (b, c). Then, the tissue is taken out from the main umbilical trocar (d, e). Removed endometriotic cyst mass (f)

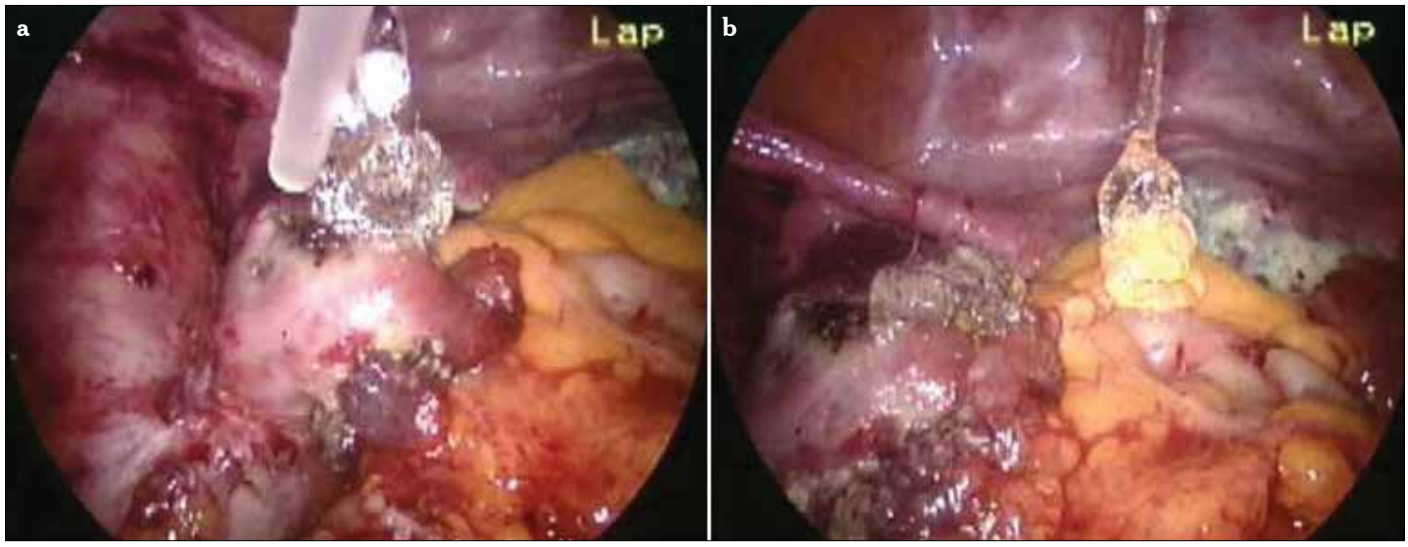

Figure 12. a, b. Adhesion barrier gel can be applied to the field to prevent subsequent surgery-related adhesion formation

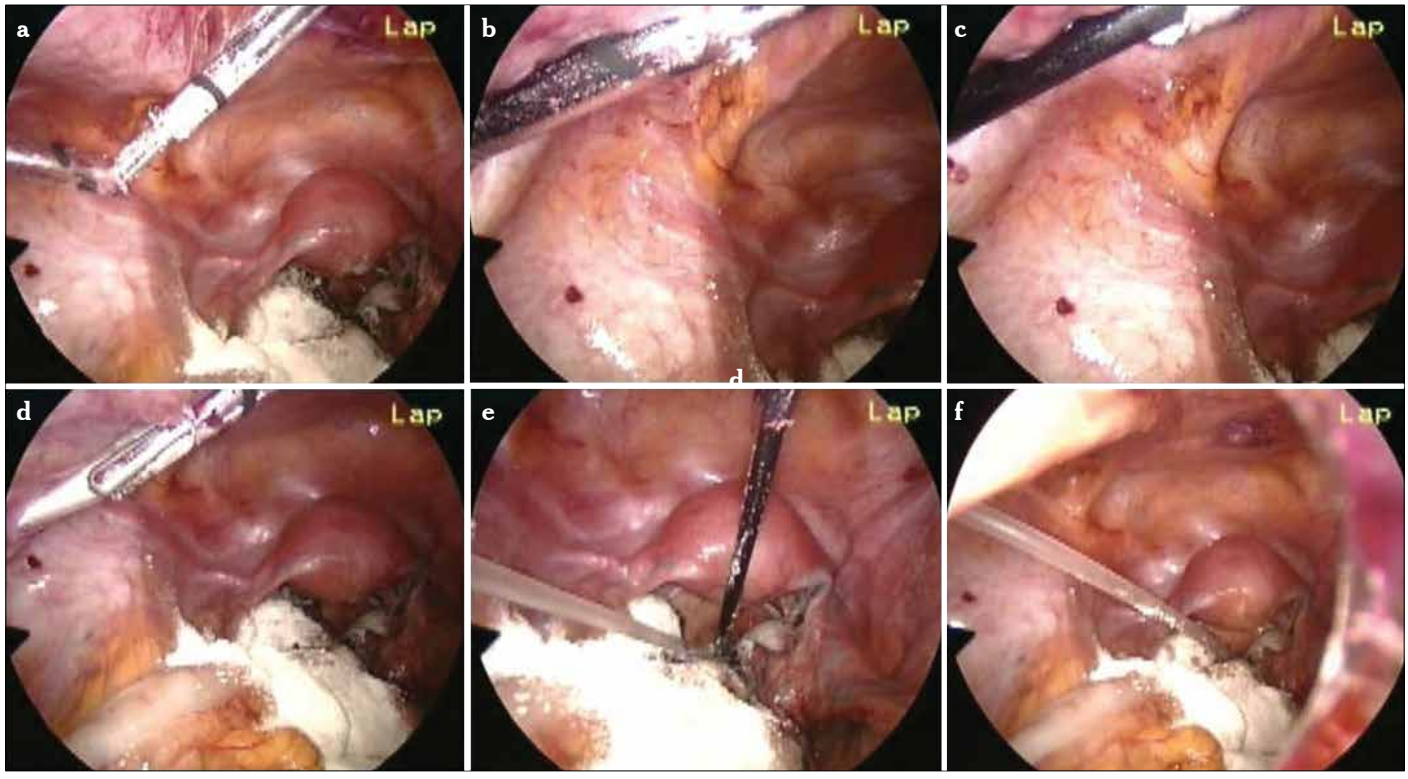

Figure 13. a-f. When necessary, a 14-16 F rubber drain can be applied after cessation of the operation. A grasper with teeth is introduced from one ancillary trocar to the others (a). When the tip of the grasper reaches the outside, this trocar is taken out, and the tip of the drain is grasped with the grasper (b, c). Then, the grasper is pulled back to introduce the drain into the pouch of Douglas (d, e). Final appearance (f)

present to confirm the diagnosis histologically, reduce the risk of infection, improve access to follicles, and possibly improve ovarian response. The woman should be counseled regarding the risks of reduced ovarian function after surgery and the loss of the ovary. The decision should be reconsidered if she has had previous ovarian surgery. If it is possible, the technique should standardized. The endoscopic treatment of an endometrioma is a relatively simple procedure and requires specific training, just as it does to learn the treatment by laparotomy. To start the surgical procedure, a surgeon needs a detailed description, including instruments, patient selection, installation, and steps in the procedures, as well as the difficulties. The level of expertise in endometriosis surgery is inversely correlated with inadvertent removal of healthy ovarian tissue along with the endometrioma capsule. In inexperienced hands, cystectomy can be destructive to the ovary, whereas ablation may be incomplete, with a

greater risk of recurrence. To the best of our knowledge, the modified combined technique seems to be more efficient for the treatment of endometriomas.

Author contributions: *Concept - C.Ü., G.Y.; Design - G.Y., C.Ü.; Supervision - C.Ü., G.Y.; Resource - C.Ü., G.Y.; Materials - G.Y., C.Ü.; Data Collection&/or Processing - G.Y., C.Ü.; Analysis&/or Interpretation - C.Ü., G.Y.; Literature Search - G.Y., C.Ü.; Writing - G.Y., C.Ü.; Critical Reviews - C.Ü., G.Y.*

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

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

References

1. Shebl O, Ebner T, Sommergruber M, Sir A, Tews G. Anti-Muellerian hormone serum levels in women with endometriosis: a case-control study. Gynecol Endocrinol 2009; 25:713-716. [CrossRef]
2. Adamson GD. Endometriosis classification: An update. Curr Opin Obstet Gynecol 2011; 23: 213-20. [CrossRef]
3. Montagnana M, Lippi G, Danese E, Franchi M, Guidi GC. Usefulness of serum HE4 in endometriotic cysts. Br J Cancer 2009; 101: 548-58. [CrossRef]
4. Moore RG, Jabre-Raughley M, Brown AK, Robison KM, Miller MC, Allard WJ, et al. Comparison of a novel multiple marker assay vs the Risk of Malignancy Index for the prediction of epithelial ovarian cancer in patients with a pelvic mass. Am J Obstet Gynecol 2010; 203: 228-33. [CrossRef]
5. Jacob F, Meier M, Caduff R, Goldstein D, Pochechueva T, Hacker N, et al. No benefit from combining HE4 and CA125 as ovarian tumor markers in a clinical setting. Gynecol Oncol 2011; 121: 487-91. [CrossRef]
6. Huhtinen K, Suvitie P, Hiissa J, Junnila J, Huvila J, Kujari H, et al. Serum HE4 concentration differentiates malignant ovarian tumours from ovarian endometriotic cysts. Br J Cancer 2009; 100: 1315-9. [CrossRef]
7. Somigliana E, Vercellini P, Viganó P, Ragni G, Crosignani PG. Should endometriomas be treated before IVF-ICSI cycles? Hum Reprod Update 2006; 12: 57-64. [CrossRef]
8. Nagle C, Olsen C, Webb P, Jordan S, Whiteman D, Green A. Endometrioid and clear cell ovarian cancers: a comparative analysis of risk factors. Eur J Cancer 2008; 44: 2477-84. [CrossRef]
9. Ness R. Endometriosis and ovarian cancer: thoughts on shared pathophysiology. Am J Obstet Gynecol 2003; 189: 280-94. [CrossRef]
10. Garcia-Velasco JA, Somigliana E. Management of endometriomas in women requiring IVF: to touch or not to touch. Hum Reprod 2009; 24: 496-501. [CrossRef]
11. Kennedy S, Bergqvist A, Chapron C, D'Hooghe T, Dunselman G, Greb R, et al. ESHRE guideline for the diagnosis and treatment of endometriosis. Hum Reprod 2005; 20: 2698-704. [CrossRef]
12. Chapron C, Vercellini P, Barakat H, Vieira M, Dubuisson JB. Management of ovarian endometriomas. Hum Reprod Update 2002; 8: 591-7. [CrossRef]
13. Tinkanen H, Kujansuu E. In vitro fertilisation in patients with ovarian endometriosis. Acta Obstet Gynecol Scand 2000; 79: 119-22. [CrossRef]
14. Smith LP, Williams CD, Doyle JO, Closshey WB, Brix WK, Pastore LM. Effect of endometrioma cyst fluid exposure on peritoneal adhesion formation in a rabbit model. Fertil Steril 2007; 87:1173-9. [CrossRef]
15. Marana R, Caruana P, Muzii L, Catalano GF, Mancuso S. Operative laparoscopy for ovarian cysts excision vs. aspiration. J Reprod Med 1996; 41: 435-8.
16. Alborzi S, Ravanbakhsh R, Parsanezhad ME, Alborzi M, Alborzi S, Dehbashi S. A comparison of follicular response of ovaries to ovulation induction after laparoscopic ovarian cystectomy or fenestration and coagulation versus normal ovaries in patients with endometrioma. Fertil Steril 2007; 88: 507-9. [CrossRef]
17. Nezhat C, Silfen SL, Nezhat F, et al. Surgery for endometriosis. Curr Opin Obstet Gynecol 1991; 3: 385-90. [CrossRef]
18. Canis M, Pouly JL, Tamburro S, Mage G, Wattiez A, Bruhat MA. Ovarian response during IVF-embryo transfer cycles after laparoscopic ovarian cystectomy for endometriotic cysts of >3 cm in diameter. Hum Reprod 2001; 12: 2583-6. [CrossRef]
19. Marconi G, Vilela M, Quintana R, Sueldo C. Laparoscopic ovarian cystectomy of endometriomas does not affect the ovarian response to gonadotropin stimulation. Fertil Steril 2002; 78: 876-8. [CrossRef]
20. Hart R, Hickey M, Maouris P, Buckett W. Excisional surgery versus ablative surgery for ovarian endometriomata. Cochrane Database Syst Rev 2008; 16: CD004992.
21. Muzii L, Bellati F, Bianchi A, Palaia I, Manci N, Zullo M, et al. Laparoscopic stripping of endometriomas: a randomized trial on different surgical techniques. Part II. Pathological results. Hum Reprod 2005; 20: 1987-92. [CrossRef]
22. Muzii L, Bianchi A, Crocè C, Manci N, Panici PB. Laparoscopic excision of ovarian cysts: is the stripping technique a tissue-sparing procedure? Fertil Steril 2002; 77: 609-14. [CrossRef]
23. Nargund G, Cheng W, Parsons J. The impact of ovarian cystectomy on ovarian response to stimulation during in-vitro fertilization cycles. Hum Reprod 1996; 11: 81-3. [CrossRef]
24. Ho H, Lee R, Hwu Y, Lin M, Su J, Tsai Y. Poor response of ovaries with endometrioma previously treated with cystectomy to controlled ovarian hyperstimulation. J Assist Reprod Genet 2002; 19: 507-11. [CrossRef]
25. Nisolle M, Donnez J. Peritoneal endometriosis, ovarian endometriosis, and adenomyotic nodules of the rectovaginal septum are three different entities. Fertil Steril 1997; 68: 585-96. [CrossRef]
26. Donnez J, Lousse JC, Jadoul P, Donnez O, Squifflet J. Laparoscopic management of endometriomas using a combined technique of excisional (cystectomy) and ablative surgery. Fertil Steril 2010; 94: 28-32. [CrossRef]
27. Baggish MS, Tucker RD. Tissue actions of bipolar scissors compared with monopolar devices. Fertil Steril 1995; 63: 422-6.
28. Nezhat C, Nezhat F. Postoperative adhesion formation after ovarian cystectomy with and without ovarian reconstruction. Abstract O-012, 47th annual meeting of the American Fertility Association, Orlando, FL, October 21-24, 1991.
29. Operative Laparoscopy Study Group. Postoperative adhesion development after operative laparoscopy: evaluation at early second-look procedure. Fertil Steril 1991; 55: 700-4.
30. Redwine DB. Conservative laparoscopic excision of endometriosis by sharp dissection: life table analysis of reoperation and persistent or recurrent disease. Fertil Steril 1991; 56: 628-34.

Ovarian aging and premature ovarian failure

Yavuz Emre Şükür[1], İçten Balık Kıvançlı[2], Batuhan Özmen[3]

[1]Department of Obstetrics and Gynecology, Kayseri Training and Research Hospital, Kayseri, Turkey
[2]Department of Obstetrics and Gynecology, Gazimagusa State Hospital, Gazimagusa, Turkish Republic of Northern Cyprus
[3]Department of Obstetrics and Gynecology, Ankara University Faculty of Medicine, Ankara, Turkey

Abstract

Physiological reproductive aging occurs as a result of a decrease in the number and quality of oocytes in ovarian cortex follicles. Although the reason for the decrease in the quality of the pool and follicular oocytes is not fully understood, endocrine, paracrine, genetic, and metabolic factors are thought to be effective. Nowadays, in order to understand the mechanisms of ovarian aging, genomic research has gained importance. The effect of co-factors, such as telomerase and ceramide, in the ovarian aging process is only getting ascertained with new research studies. The most important tests in the assessment of ovarian aging are antral follicle count and anti-Mullerian hormone.

(J Turk Ger Gynecol Assoc 2014; 15: 190-6)

Key words: Ovarian aging, premature ovarian failure, reproduction

Received: 28 January, 2014 **Accepted:** 26 March, 2014 **Available Online Date:** 08 August, 2014

Introduction

The fertility capacity of women diminishes in parallel with aging. As the level of education of women has increased since the 1960s and they have become more active in working life and have had easier access to contraceptive methods, the need to have children has been postponed to advanced ages by more women (1, 2). As a result of the postponing of maternal age, the number of patients that are not able to get pregnant within 12 months and apply to artificial reproductive technologies (ART) with a female infertility diagnosis has been increased. Among women, the normal process of reproductive aging has great variations; some women continue to be highly fertile in their 40s, while others lose their fertility in their 30s. The process of reproductive aging in women mostly stems from the changes in ovarian function due to chronological aging. Ovaries are affected by natural aging more than all other tissues. Although the reason is not fully understood, endocrine, paracrine, genetic, and metabolic factors are thought to be affecting the decrease in the quality of the follicular pool and oocytes.

Ovarian aging resulting in ovarian failure and menopause is an on-going process. Of the early signs of ovarian aging, failure to adequately respond to ovarian stimulation, followed by menstrual irregularity and the loss of follicle functions, can be listed. In accordance with the 'fixed interval hypothesis,' the period between the first menstrual cycle irregularities and menopause is constant-approximately 6 years-and is independent from the age of menopause (3, 4). It is believed that the process of physiological reproductive aging stems from the decrease in the number and quality of the oocytes in the ovarian cortex follicles. This reduction process in the oocytes accelerates with aging and increases especially after the age of 38 with a biphasic pattern (5). The monthly fecundity decreases approximately from the age of 30 (6, 7). The first but inconspicuous sign of reproductive aging process is 2-3 days of shortening of the menstrual cycle (8). Menopausal transition is defined as the stage of ovarian aging and starts approximately at the age of 46 (8). The last menstrual period (menopause) is expected approximately at the age of 51 (range 40-60) and is considered as the physiological sequel of ovarian aging (9, 10). In the last century, in spite of the increase in life expectancy and decrease in menarche age, there has been no significant change in menopausal age. It is thought that genetic control is important and that environmental factors are effective in determining the natural menopausal age (11).

Endocrinological Factors in Ovarian Aging

During reproductive life, the length of a regular menstrual cycle is typically 28 days. The increase in the early follicular FSH level before the onset of menstrual irregularity during the menopausal transition period may point out a decrease in the number follicles. During the menopausal transition period, the menstrual cycles worsen further due to the decrease in the FSH-sensitive follicles. As a result of the selection of dominant follicles, the follicular phase shortens (12). Then, the delay in the development of dominant follicles or withdrawal of estrogen without corpus luteum function causes extended cycles and anovulatory hemorrhages (13).

Address for Correspondence: Batuhan Özmen, Department of Obstetrics and Gynecology, Ankara University Faculty of Medicine, Ankara, Turkey
Phone: +90 312 595 64 05 e.mail: batuhanozmen@gmail.com

DOI:10.5152/jtgga.2014.0022

As a result of the declining cohort of antral follicles, first inhibin B secretion decreases, then estradiol, and finally inhibin A secretion. This then results in changes in the feedback mechanism. In the menopausal transition stage, a clear decrease in inhibin B levels can be noted along with further increases in FSH levels, and this indicates a decreased number of antral follicles (14). Estradiol and inhibin A levels remain largely unaltered until the later stages of the menopausal transition. Only when periods of amenorrhea become lengthy will levels of these hormones decrease and contribute to the loss of negative ovarian feedback in the late stages of ovarian aging (15). Luteal phase endocrinology does not significantly change with advancing age. In case ovulation still occurs, the secretion of estradiol, progesterone, and inhibin A from the corpus luteum seems unaltered (16). In late-reproductive-period women who still have regular menstrual cycles, elevations of FSH affect ovarian function. The elevated early follicular FSH levels will often drive more than one single follicle into dominance, resulting in elevated early follicular estradiol levels and the increased occurrence of dizygotic twinning (17).

During early fetal development, human oocytes initiate meiosis. Oocytes subsequently enter prophase, and genetic material is exchanged between homologous chromosomes (recombination). Following that, oocytes progress to the diplotene phase, but this process pauses at meiosis 1 (MI) (18). At this stage, oocytes are surrounded by a single layer of granulosa cells, forming the primordial follicle. Primordial follicles generally remain quiescent for years. The initial follicular maturation from the resting primordial follicle to the Graafian preovulatory follicle takes several months. The majority of follicles enters atresia at some stage during this maturation process (19). The follicular meiotic division is only completed with ovulation, which is induced by the mid-cycle LH increase. One group of chromosomes remains in the oocyte, whereas the other is segregated in the first polar body. By the completion of this first division, the number of chromosomes is reduced to half. Only in the case of fertilization is the second division completed (MII). Hence, all steps are under the influence of certain signals, and the entire process may last many decades. It is suggested that oocyte-derived factors, such as growth differentiation factor 9 (GDF9) or bone morphogenetic protein 15 (BMP15) may be effective in regulating folliculogenesis (20, 21).

Genetic Factors in Ovarian Aging

The association between menopausal age of mothers and daughters and also between sisters has suggested that the genetic factors are effective on the reproductive aging process. The heritability for age at menopause is estimated to range from 30% to 85% (22). Premature ovarian failure (POF) cases without an obvious cause may be considered to be part of the variation of menopause, and therefore, POF may offer a unique model for the study of the genetic mechanisms of ovarian aging. Genes, like FSH, FSHR, LH, LHR, CYP17, and CYP19, that exert known hormonal effects primarily affect follicle function, whereas genes like BMP15, GDF9, and GPR3 affect the rate of initial selection from the primordial follicle pool. Mutations and small variations in these genes could result in the decrease of the life of the follicle pool and the reproductive life span (23, 24). Genes expressed during oogenesis may lead to various degrees of germ cell formation. These genes include DNA-binding proteins and transcription factors, like NOBOX (newborn ovary homeobox) and LHX8, and RNA-binding proteins, like NANOS. NOBOX, GDF9, and LDX8 mutations directly causing POF have indeed been identified in few women (25). Recently, the first genome-wide association analysis has revealed that POF is linked to the ADAMts9 gene (26). Two chromosomal regions have been determined with a genome-wide scan carried out on sibling sisters: 9q21.3 and Xp21.3 (27). In more than 28% of femail fragile X permutation carriers, POF occurs, and a gene at chromosome 9 linkage region encodes for a member of the BCL2 family, which is involved in apoptosis (28, 29). In genome-wide studies on menopausal women, it has been determined that several single-gene polymorphisms on chromosomes 5, 6, 13, 19, and 20 are associated with menopausal age (30, 31). Micro-deletions involving GDF9, BMP15, and FOXL2 have been shown to produce early ovarian arrest (32-34). Also, the estrogen-inactivating polymorphism CYP1B1-4 appears to have relations with early menopausal age (35). With this polymorphism, higher levels of estrogens throughout the reproductive life are believed to exist, but the way in which this would affect the ovarian follicular pool remains to be elucidated. Common polymorphisms in the gene for AMH receptor 2 have been associated with age at menopause in two large cohorts. Less active AMH signaling would lead to weaker inhibition of initial follicle recruitment, resulting in a possible increased rate of follicle loss (36).

Mitochondrial energy production has a key role in cell proliferation and apoptosis. The mitochondria's own genetic material (mtDNA) is inherited maternally. Increase in mtDNA deletions in luteinizing granulosa cells after the age of 38 shows a reduction in the levels of antioxidant enzymes and consequently accelerates apoptosis in oocytes with the increase of certain factors, such as ceramide (37, 38). Ca^{2+} fluctuations in abnormal mitochondria will not stimulate the production of ATP, which supports the normal physiological process, and fertility is affected.

Micro-environmental Factors in Ovarian Aging

Telomeres are DNA nucleotide sequences and specific proteins located at the ends of all eukaryotic chromosomes. Telomeres in human beings consist of repetitive several thousand consecutive pieces of TTAGGG double-stranded sequence. Telomeric DNA normally terminates with a single strand at the 3' end. This particular configuration blocks end-to-end binding of the chromosomes and provides protection. However, in each chromosome replication, depending on the end replication problems, 100-200 base pairs (bp) of telomeric DNA is lost, and gradually, telomeres become shorter (39). Telomeres in humans regress from 10-15 kilobases (kb) to 2-5 kb during a life span. For this reason, telomeres are also known as a mitotic clock, and the remaining telomeres show the proliferative capacity of a cell. The telomere end replication problem is solved by the telomerase enzyme complex. Telomerase is an RNA enzyme connected to telomeres and provides protection and positively

contributes to its length (40). With aging, telomerase activity is reduced in human ovarian cells (41). Telomerase activity was detected especially in early antral and preovulatory follicles, as well as ovulated oocytes, but a significant decrease is observed with maturation (42, 43). Although there is no correlation between telomerase and FSH levels, telomerase activity may be a good indicator for the functional age of the ovary.

Reactive oxygen and nitrogen species produced during biological metabolism are referred to as free radicals. According to the generally accepted theory, intramitochondrial electron leakage occurs as a result of age-related decrease in cellular respiration, and this impairs mtDNA stability and mitochondrial function (44). Oxidative stress occurs when the production of free radicals exceeds the cleaning capability of antioxidants. This imbalance creates oxidative damage and ultimately leads to the release of cytochrome c and other apoptosis-stimulating factors. Thus, cell death occurs (45, 46). Oxidative stress due to aging in a sense is caused by the weakening of the antioxidant enzymatic defense. Glutathione (GSH) and glutathione transferase (GST), which are effective in the removal of free radicals, are reduced in oocytes with age (47). With the weakening of the antioxidant defense, aging occurs in granulosa cells, accompanied by Cu/Zn superoxide dismutase, Mn superoxide dismutase, and catalase down-regulation (48). As a result, the increase in oxidative damage associated with the weakening of antioxidant defense mechanisms causes aging of the ovaries.

Ceramide, which is a precursor of the sphingolipid secondary messenger, is responsible for cellular silence and physical aging (49). In female germ cells, an increase in apoptosis is observed with aging, and this requires communication between the oocyte and the surrounding cumulus cells. In animal experiments, it is indicated that with aging, ceramides exit the cumulus cells and pass to the neighboring oocyte and initiate apoptosis, and it is also shown that this incident may be prevented by sphingosine-1-phosphate (38). This exchange of ceramide is only possible if there is a gap-junction and a complete lipid transport system between the cumulus cells and the oocyte. In addition, in oocyte susceptibility to ceramide increases with aging (38).

Formation of advanced glycation end-products (AGEs) is an irreversible process that increases with cases, such as aging, atherosclerosis, and diabetes mellitus. AGEs cause tissue damage by protein cross-linkage or by connecting special receptors, called RAGE (receptor for advanced glycation end-products) (50). AGE-RAGE connection causes cellular oxidative stress. Ovarian dysfunction due to AGEs might relate to ART outcomes and measures of ovarian reserve (51).

The level of oxygen provided by perifollicular vascularization and paracrine regulators is necessary for a healthy micro-environment. The fertilization and development potential of oocytes with complete vascularization and high levels of oxygen (≥3%) are higher (52, 53). Increased perifollicular vascularization in IVF patients increases the rate of live births (54).

Assessment of Ovarian Aging

Nowadays, methods of ultrasonographic assessment of ovarian aging include antral follicle count, ovarian volume, and ovarian blood flow measurement. During ART, in order to assess the ovarian response, antral follicle count is more sensitive to ovarian volume measurements (55). However, both ultrasound tests have low predictive values for pregnancy. Clinically, the most widely used test is antral follicle count, as this test is easy, cheap, and reliable. The decreasing stromal blood flow of women with low ovarian reserve is monitored by Doppler ultrasonography. Doppler ultrasound measurement of blood flow can be used as a marker of premature ovarian aging in the future.

Traditional tests that are used to assess the ovarian reserve of patients undergoing ART include the basal follicle-stimulating hormone (FSH) in early follicular phase, estradiol, inhibin B, and FSH/luteinizing hormone (LH) ratio. High FSH level is an irrefutable marker for ovarian aging; however, it increases 10 years prior to menopause or when infertility occurs. Therefore, it is not a very useful test. In addition, estradiol and inhibin A levels in the early follicular phase are stable until late menopausal transition period and therefore must not be used as a test of ovarian aging. In addition, these tests have low predictive values for pregnancy and ovarian response. Anti-Müllerian hormone (AMH) and inhibin B are members of the TGF-B (transforming growth factor-B) family. AMH is an important ovarian aging test for the evaluation of follicular pool. It is expressed as early as the 36th gestational week, and serum levels are gradually increased in the first 3-4 years and become stable until puberty (56). AMH, which is a dimeric glycoprotein, is secreted to the serum from the granulosa cells of early developing follicles, especially from pre-antral and small antral follicles. It has a strong correlation with the antral follicle count (57). Early stages of follicular development are mainly inhibited by AMH. One of the major advantages of the AMH test is that the serum levels remain constant throughout the entire menstrual cycle (58). AMH becomes undetectable approximately 5 years before menopause occurs (59). It has high predictive value for poor ovarian response in clinical practice, for cycle cancellation, excessive ovarian response, and ovarian hyperstimulation syndrome (60). However, the importance is not yet certain for embryo quality, implantation, and pregnancy rates. Inhibin B is mainly secreted from FSH-sensitive antral follicles. The shrinkage of this cohort with advancing age will cause inhibin B levels to decrease. The dynamic tests for ovarian aging include clomiphene citrate challenge test (CCCT) and GnRH agonist stimulation test. However, the dynamic tests are not frequently used, as they take a longer time and are expensive and complicated. In addition, there is no superiority of these tests from the described static tests (61).

Genome-wide studies have been conducted to investigate ovarian aging-related genes, including particular candidate genes. But, as yet, there is no test that can be used in routine practice. Another strategy is to investigate the genetic disorders known to POF. This group covers 20%-25% of the patients previously classified as idiopathic (62). The most common genetic disorders include X chromosome abnormalities, FMR1 premutation, and the more recently identified BMP15, FIGLA, GDF9, and NR5A1 gene mutations (62).

Premature Ovarian Failure

In women, primary hypogonadism is defined as ovarian insufficiency accompanied by high serum levels of FSH. POF, which is also referred to as primary ovarian insufficiency, is primary hypogonadism before the age of 40. POF is characterized by loss of follicles, folliculogenesis, estrogen production, and infertility. It is not essential to observe amenorrhea for the diagnosis of POF, as spontaneous menstrual cycles can be seen after the diagnosis as well. The disorder affects approximately 1% of women below the age of 40 and 0.1% before the age of 30 (63). The incidence is 10%-28% in women with primary amenorrhea and 4%-18% in women with secondary amenorrhea (64). Most of these patients undergo a normal pubertal process and regular menstrual cycles. Irregularity in the menstrual cycle is the most common symptom. In women diagnosed with POF, estrogen production and ovulation can be seen. Normal pregnancy may occur in 5%-10% of these patients (65).

Etiology

Approximately 20%-30% of the relatives of POF patients are also affected (66). The genetic causes of POF include X chromosome abnormalities and single gene disorders. Defects of the X chromosome include partial deletion, translocations, and missing or extra chromosomes. Turner syndrome is mosaic or complete monosomy of the X chromosome. Both X chromosomes are required for the completion of oogenesis; therefore, ovarian function is defective in Turner syndrome. Although it is difficult to assess the exact locus, it is thought that it may be due to a defect in the Xp11.2-p22.1 region (67). Trisomy X syndrome (47,XXX) is caused by the attachment disorder of the X chromosome during maternal meiosis, and this may cause POF, too (68). Mental retardation, growth retardation, tremor, ataxia, and dementia are observed in fragile X syndrome premutation carriers; 16%-21% of these patients are at risk of POF (69). It has recently been thought that 6% of POF patients are fragile X carriers (70). CGG triplet repeats of the first exon of the X-linked FMR1 (familial mental retardation-1) gene cause fragile X syndrome. Premutation is defined as between 50 to 200 repeats. POF risk is higher when the premutation is transferred from the father (28%) than the mother (4%) (71). While the frequency of the FMR1 premutation is 14% for familial POF patients, this rate is 2% for sporadic cases (69, 72). Single-gene disorders include FSH and LH receptor mutations, inhibin mutations, and galactosemia. A particular FSH receptor mutation (566C>T) causes ovarian failure and amenorrhea in some Finnish families (73). Mutations in the inhibin α and β genes cause severe symptoms of POF. Amenorrhea at the age of 10 occurs in 7% of patients (74). An INHA G769A special mutation is detected in approximately 5% of patients with POF (75). Galactosemia is an autosomal recessive disease, and 80% of patients develop POF (76). As a result of a galactose-1-phosphate uridyl transferase gene mutation, the accumulated toxic level of galactose metabolites in the ovaries develops POF. There are many other autosomal gene loci identified in patients with POF. Mutation of the FOXL2 transcription factor gene, which is located on chromosome 3, is one of the causes of POF (77). Also, BMP15, GDF9, phosphomannomutase 2 (PMM2), FRAXA, and POF1B gene mutations are causes of POF (78-80).

Table 1. Gonadotoxic risks of chemotherapeutic agents

High risk	Medium risk	Low risk or no risk
Cyclophosphamide	Cisplatin	Methotrexate
Busulfan	Adriamycin	5-Fluorouracil
Melphalan	Paclitaxel (needs more studies)	Actinomycin D
Procarbazine		Bleomycin
Nitrogen mustard		Vincristine
Chlorambucil		

Three enzymatic defects in the steroidogenic pathway cause hypergonadotropic amenorrhea. These are 17α-hydroxylase (17,20-lyase), 20,22-lyase, and aromatase deficiencies. 17α-hydroxylase deficiency can be easily detected, as it develops primary amenorrhea, absence of secondary sexual characteristics, hypergonadotropism, hypertension, hypokalemic alkalosis, and increased levels of deoxycorticosterone and progesterone (81).

In 15%-20% of patients with POF, an autoimmune disease is also present (82). Autoimmune POF can be seen as isolated or as part of autoimmune polyglandular diseases. More than 60% of these syndromes develop ovarian failure. Type 1 autoimmune polyglandular syndrome is rare and occurs at a young age and is autosomal recessively inherited. It causes hypoparathyroidism, mucocutaneous candidiasis, primary hypogonadism, and hypoadrenalism. Polyglandular autoimmune syndrome type 2 is more common, seen in adult patients, and has polygenic inheritance associated with HLA-DR3 and HLA-DR4. It causes adrenal insufficiency, autoimmune thyroid disease, type 1 diabetes, and gonadal failure. In patients with POF, other autoimmune diseases, such as vitiligo, myasthenia gravis, Sjögren's syndrome, systemic lupus erythematosus, celiac disease, rheumatoid arthritis, and pernicious anemia, may occur. In 11% of patients with POF, lymphocytic oophoritis is present, and steroid cell antibodies are present in 78% (83). Steroid cell antibodies seen in Addison's disease damage the granulosa/theca interna cells of the ovarian follicles. In 3% of patients with POF, adrenal insufficiency develops (300 times that of the general population) (84). In 90% of these patients, POF develops prior to adrenal insufficiency (85).

Chemotherapy and radiation therapy for the treatment of malignant diseases are the most common causes of POF. The effects of chemotherapy are dose- and drug-dependent (Table 1). Chemotherapy reduces the number of oocytes by damaging the DNA and disrupts the structure and function of the oocyte and granulosa cells. POF due to chemotherapeutics may be temporary; however, spontaneous recovery of ovarian function is less likely in elderly patients. In order to reduce the gonadotoxic effects of chemotherapy, simultaneous provision of GnRH analogs may be helpful (86). Radiotherapy affects the ovaries, depending on the radiation area. Radiation dose and age are other effective factors. Prepubertal ovaries are relatively more resistant to radiation (87). Approximately 2 weeks after the beginning of radiotherapy, steroid levels reduce and gonadotro-

pins increase. Laparoscopic ovarian transposition before pelvic radiation therapy reduces the risk of POF (88). Hormone treatments have no effect on reducing the risk.

Premature ovarian failure may also develop due to mumps oophoritis. In these patients, mainly menstrual cycle disorders and infertility occur. Although there is no conclusive evidence, smoking may lead to POF, too. The idiopathic POF is a diagnosis of exclusion, and it is preferred when no other causes are ascertained; 75% to 90% of all patients are still in this group (89).

Assessment of patients with POF

Young women missing at least three consecutive menstrual cycles should be assessed. Patients diagnosed with POF should be asked in terms of both family history of mental retardation and POF. Hearing impairment may be associated with Perrault syndrome. Dry eye should be questioned in terms of autoimmune diseases. Previous operations; viral infections; treatments, such as chemotherapy and radiotherapy; and smoking should also be questioned.

In women younger than 40, at least two menopausal FSH levels (>40 IU/L) will be sufficient for the diagnosis of POF. The first tests to be made in these patients to distinguish other hormonal reasons are FSH, estradiol, prolactin, and TSH measurement. The aim of the basal LH measurement is to evaluate the presence of functional follicles. Overall, if estradiol is above 50 pg/mL and LH level is above the level of FSH, this is an indication that there are at least several live follicles. Nowadays, anti-ovarian antibodies are not considered to be valuable, and it is more important to investigate the anti-adrenal antibodies, as patients with POF develop adrenal insufficiency 300 times more often than the general population. Also, in terms of autoimmune thyroid diseases, it is appropriate to carry out thyroid function tests. Today, the patients with POF of unknown cause are suggested to be assessed in terms of FMR1 premutation (90). Especially in patients younger than the age of 30 or patients with primary amenorrhea, karyotype analysis must be carried out. Further tests may be carried out, depending on other clinical suspicions, such as galactosemia.

Transvaginal or pelvic ultrasound is important for the antral follicle count. Antral follicles are round or oval-shaped anechoic structures 5-10 mm in diameter. Ultrasound is important in the identification of the internal genitalia of primary amenorrheic patients and also, if necessary, in order to display the streak gonads. Ovarian biopsy is not necessary in patients with POF and normal karyotype.

Management

Behavioral changes, such as quitting smoking, should be accomplished primarily in order to reduce the risk of premature ovarian failure. Laparoscopic ovarian transposition before pelvic radiotherapy is likely to prevent ovarian failure. In order to prevent chemotherapy-induced and age-related follicle loss, hormonal manipulation has become widespread in recent years (91). Also, cryopreservation of ovarian tissue prior to chemotherapy is still accepted as an experimental method but is getting popular recently (92).

Exogenous hormone replacement therapy (HRT) should be recommended to patients to prevent menopausal symptoms, bone mineral density loss, and cardiovascular endothelial function deterioration. Although patients take HRT, they should be warned in terms of contraception if they do not wish to get pregnant. After diagnosis, spontaneous ovulation may occur in 25% of POF patients, and pregnancy may occur in 10%, regardless of the treatment (90). It is recommended that barrier protection methods be used despite oral contraceptives if the patients do not want pregnancy. It is not yet understood how these patients can ovulate and conceive under such treatment with high doses of steroids. It is more appropriate to give exogenous estrogen and cyclic progesterone to POF patients. For this purpose, applying transdermal 17β-estradiol (initial dose 0.1 mg) and 100 mg of micronized progesterone for 14 days is considered a good treatment regimen.

Unfortunately, the chance of success of ART in patients with POF is low. Even after the suppression of gonadotropin, ovulation induction, spontaneous ovulation, and pregnancy rates can not be captured (93). Although not legal in our country, in some developed countries, the chance of pregnancy is increased in these patients with oocyte donation.

Ethics Committee Approval: *N/A.*

Informed Consent: *N/A.*

Peer-review: *Externally peer-reviewed.*

Author contributions: *Concept - B.Ö.; Design - B.Ö., Y.E.Ş.; Supervision - B.Ö.; Resource - B.Ö.; Materials - Y.E.Ş., B.Ö.; Data Collection&/or Processing - İ.B.K, Y.E.Ş., B.Ö.; Analysis&/or Interpretation - İ.B.K., Y.E.Ş., B.Ö.; Literature Search - İ.B.K., Y.E.Ş.; Writing - İ.B.K., Y.E.Ş., B.Ö.; Critical Reviews - B.Ö.*

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

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

References

1. Leridon H. Demographic effects of the introduction of steroid contraception in developed countries. Hum Reprod Update 2006; 12: 603-16. [CrossRef]
2. te Velde ER, Pearson PL. The variability of female reproductive ageing. Hum Reprod Update 2002; 8: 141-54. [CrossRef]
3. Lisabeth L, Harlow S, Qaqish B. A new statistical approach demonstrated menstrual patterns during the menopausal transition did not vary by age at menopause. J Clin Epidemiol 2004; 57: 484-96. [CrossRef]
4. Den Tonkelaar I, te Velde ER, Looman CW. Menstual cycle lenght preceding menopause in relation to age at menopause. Maturitas 1998; 29: 115-23. [CrossRef]
5. Faddy MJ, Gosden RG, Gougeon A, Richardson SJ, Nelson JF. Accelerated disappearance of ovarian follicles inmidlife: Implications for forecasting menopause. Hum Reprod 1992; 7: 1342-6.
6. Schwartz D, Mayaux MJ. Female fecundity as a function of age: Results of artificial insemination in 2193 nulliparous women with azoospermic husbands. Federation CECOS. N Engl J Med 1982; 306: 404-6. [CrossRef]

7. van Noord-Zaadstra BM, Looman CW, Alsbach H, Habbema JD, te Velde ER, Karbaat J. Delaying childbearing: effect of age on fecundity and outcome of pregnancy. BMJ 1991; 302: 1361-5. [CrossRef]
8. Treloar AE, Boynton RE, Behn BG, BrownBW. Variation of the human menstrual cycle through reproductive life. Int J Fertil 1967; 12: 77-126.
9. Broekmans FJ, Faddy MJ, Scheffer G, te Velde ER. Antral follicle counts are related to age at natural fertility loss and age at menopause. Menopause 2004; 11: 607-14. [CrossRef]
10. Treloar AE. Menstrual cyclicity and the pre-menopause. Maturitas 1981; 3: 249-64.[CrossRef]
11. De Bruin JP, Bovenhuis H, Van Noord PAH, Pearson PL, van Arendonk JA, te Velde ER, et al. The role of genetic factors in age at natural menopause. Hum Reprod 2001; 16: 2014-8. [CrossRef]
12. van Zonneveld P, Scheffer GJ, Broekmans FJ, Blankenstein MA, de Jong FH, Looman CW, et al. Do cycle disturbances explain the age-related decline of female fertility? Cycle characteristics of women aged over 40 years compared with a reference population of young women. Hum Reprod 2003; 18: 495-501. [CrossRef]
13. Burger HG, Hale GE, Dennerstein L, RobertsonDM. Cycle and hormone changes during perimenopause: the key role of ovarian function. Menopause 2008; 15: 603-12.[CrossRef]
14. de Koning CH, McDonnell J, Themmen AP, de Jong FH, Homburg R, Lambalk CB. The endocrine and follicular growth dynamics throughout the menstrual cycle in women with consistently or variably elevated early follicular phase FSH compared with controls. Hum Reprod 2008; 23: 1416-23. [CrossRef]
15. Hoekstra C, Zhao ZZ, Lambalk CB, Willemsen G, Martin NG, Boomsma DI, Montgomery GW. Dizygotic twinning. Hum Reprod Update 2008; 14: 37-47. [CrossRef]
16. Burger H. The menopausal transition- endocrinology. J Sex Med 2008; 5: 2266-73.
17. Beemsterboer SN, Homburg R, Gorter NA, Schats R, Hompes PG, Lambalk CB. The paradox of declining fertility but increasing twinning rates with advancing maternal age. Hum Reprod 2006; 21: 1531-2. [CrossRef]
18. Mehlmann LM. Stops and starts in mammalian oocytes: Recent advances in understanding the regulation of meiotic arrest and oocyte maturation. Reproduction 2005; 130: 791-9. [CrossRef]
19. Gougeon A. Regulation of ovarian follicular development in primates: Facts and hypotheses. Endocr Rev 1996; 17: 121-55. [CrossRef]
20. Andreu-Vieyra C, Lin YN, Matzuk MM. Mining the oocyte transcriptome. Trends Endocrinol Metab 2006; 17: 136-43. [CrossRef]
21. Gilchrist RB, Lane M, Thompson JG. Oocyte-secreted factors: regulators of cumulus cell function and oocyte quality. Hum Reprod Update 2008; 14: 159-77. [CrossRef]
22. Wicks J, Treloar SA, Martin NG. Using identity-bydescent information in affected sib pairs to increase the efficiency of genetic association studies. Twin Res 2004; 7: 211-6. [CrossRef]
23. Kok HS, van Asselt KM, van der Schouw YT, Peeters PH, Wijmenga C. Genetic studies to identify genes underlying menopausal age. Hum Reprod Update 2005; 11: 483-93. [CrossRef]
24. Wang TT, Ke ZH, Song Y, Chen LT, Chen XJ, Feng C. Identification of a mutation in GDF9 as a novel cause of diminished ovarian reserve in young women. Hum Reprod 2013; 28: 2473-81. [CrossRef]
25. Skillern A, Rajkovic A. Recent developments in identifying genetic determinants of premature ovarian failure. Sex Dev 2008; 2: 228-43. [CrossRef]
26. Knauff EA, Franke L, van Es MA, van den Berg LH, van der Schouw YT, Laven JSE, et al. Genome-wide association study in premature ovarian failure patients suggests ADAMTS19 as a possible candidate gene. Hum Reprod 2009; 24: 2372-8. [CrossRef]
27. Li Q, Geng XD, Zheng W, Tang J, Xu B, Shi QH. Current understanding of ovarian aging. Life Sci 2012; 55: 655-9.
28. Welt CK, Smith PC, Taylor AE. Evidence of early ovarian aging in fragile X premutation carriers. J Clin Endocr Metab 2004; 89: 4569-74. [CrossRef]
29. Hsu SY, Hsueh AJW. Tissue-specific Bcl-2 protein partners in apoptosis: An ovarian paradigm. Physiol Rev 2000; 80: 593-614.
30. He CY, Kraft P, Chen C, Buring JE, Paré G, Hankinson SE, et al. Genome-wide association studies identify loci associated with age at menarche and age at natural menopause. Nat Genet 2009; 41: 724-8. [CrossRef]
31. Stolk L, Zhai G, van Meurs JB, Verbiest MM, Visser JA, Estrada K, et al. Loci at chromosomes 13, 19 and 20 influence age at natural menopause. Nat Genet 2009; 41: 645-7. [CrossRef]
32. Willer CJ, Scott LJ, Bonnycastle LL, Jackson AU, Chines P, Pruim R, et al. Tag SNP selection for Finnish individuals based on the CEPH Utah HapMap database. Genet Epidemiol 2006; 30: 180-90. [CrossRef]
33. International HapMap Consortium. A haplotype map of the human genome. Nature 2005; 437: 1299-320. [CrossRef]
34. Lakhal B, Laissue P, Braham R, Elghezal H, Saâd A, Fellous M, Veitia RA. BMP15 and premature ovarian failure: causal mutations, variants, polymorphisms? Clin Endocrinol (Oxf) 2010; 72: 425-6. [CrossRef]
35. Weel AE, Uitterlinden AG, Westendorp IC, Burger H, Schuit SC, Hofman A, et al. Estrogen receptor polymorphism predicts the onset of natural and surgical menopause. J Clin Endocrinol Metab 1999; 84: 3146-50. [CrossRef]
36. Kevenaar ME, Themmen AP, Rivadeneira F, Uitterlinden AG, Laven JS, van Schoor NM, et al. A polymorphism in the AMH type II receptor gene is associated with age at menopause in interaction with parity. Hum Reprod 2007; 22: 2382-8. [CrossRef]
37. Tatone C, Carbone MC, Falone S, Aimola P, Giardinelli A, Caserta D, et al. Age-dependent changes in the expression of superoxide dismutases and catalase are associated with ultrastructural modifications in human granulosa cells. Mol Hum Reprod 2006; 12: 655-60. [CrossRef]
38. Perez GI, Jurisicova A, Matikainen T, Moriyama T, Kim MR, Takai Y, et al. A central role for ceramide in the age-related acceleration of apoptosis in the female germline. FASEB J 2005; 19: 860-2.
39. Olovnikov AM. Telomeres, telomerase, and aging: Origin of the theory. Exp Gerontol 1996; 31: 443-8. [CrossRef]
40. Rhyu MS. Telomeres, telomerase and immortality. J Natl Cancer Inst 1995; 87: 884-94. [CrossRef]
41. Kinugawa C, Murakami T, Okamura K, Yajima A. Telomerase activity in normal ovaries and premature ovarian failure. Tohoku J Exp Med 2000; 190: 231-8. [CrossRef]
42. Betts DH, King WA. Telomerase activity and telomere detection during early bovine development. Dev Genet 1999; 25: 397-403. [CrossRef]
43. Yamada-Fukunaga T, Yamada M, Hamatani T, Chikazawa N, Ogawa S, Akutsu H, et al. Age-associated telomere shortening in mouse oocytes. Reprod Biol Endocrinol 2013; 11: 108-18. [CrossRef]
44. Miquel J, Economos A C, Fleming J, Johnson JE Jr. Mitochondrial role in cell aging. Exp Gerontol 1980; 15: 575-91. [CrossRef]
45. Vercesi AE, Kowaltowski AJ, Oliveira HC, Castilho RF. Mitochondrial Ca2+ transport, permeability transition and oxidative stress in cell death: Implications in cardiotoxicity, neurodegeneration and dyslipidemias. Front Biosci 2006; 11: 2554-64. [CrossRef]
46. Tatone C, Amicarelli F, Carbone MC, Monteleone P, Caserta D, Marci R, et al. Cellular and molecular aspects of ovarian follicle ageing. Hum Reprod Update 2008; 14: 131-42. [CrossRef]
47. Van Blerkom J. The influence of intrinsic and extrinsic factors on the developmental potential and chromosomal normality of the human oocyte. J Soc Gynecol Investig 1996; 3: 3-11.[CrossRef]
48. Carbone MC, Tatone C, Delle Monache S, Marci R, Caserta D, Colonna R, Amicarelli F. Antioxidant enzymatic defences in human follicular fluid: Characterization and age-dependent changes. Mol Hum Reprod 2003; 9: 639-43. [CrossRef]

49. Kolesnick RN, Krönke M. Regulation of ceramide production and apoptosis. Annu Rev Physiol 1998; 60: 643-65. [CrossRef]
50. Schmidt AM, Yan SD, Yan SF, Dtern DM. The biology of the receptor for advanced glycation end products and its ligands. Biochim Biophys Acta 2000; 1498: 99-111. [CrossRef]
51. Merhi Z. Advanced glycation end products and their relevance in female reproduction. Hum Reprod 2014; 29: 135-45.[CrossRef]
52. Redmer DA, Reynolds LP. Angiogenesis in the ovary. Rev Reprod 1996; 1: 182-92. [CrossRef]
53. Huey S, Abuhamad A, Barroso G, Hsu MI, Kolm P, Mayer J, Oehninger S. Perifollicular blood flow doppler indices, but not follicular po2, pco2, or ph, predict oocyte developmental competence in in vitro fertilization. Fertil Steril 1999; 72: 707-12. [CrossRef]
54. Borini A, Maccolini A, Tallarini A, Bonu MA, Sciajno R, Flamigni C. Perifollicular vascularity and its relationship with oocyte maturity and IVF outcome. Ann N Y Acad Sci 2001; 943: 64-7. [CrossRef]
55. Broekmans FJ, de Ziegler D, Howles CM, Gougeon A, Trew G, Olivennes F. The antral follicle count: practical recommendations for better standardization. Fertil Steril 2010; 94: 1044-51. [CrossRef]
56. Mutlu MF, Erdem A. Evaluation of ovarian reserve in infertile patients. J Turk Ger Gynecol Assoc 2012; 13: 196-203. [CrossRef]
57. Göksedef BP, Idiş N, Görgen H, Rüstemoğlu Asma Y, Api M, Çetin A. The correlation of the antral follicle count and serum anti-mullerian hormone. J Turk Ger Gynecol Assoc 2010; 11: 212-5. [CrossRef]
58. La Marca A, Broekmans FJ, Volpe A, Fauser BC, Macklon NS; ESHRE Special Interest Group for Reproductive Endocrinology--AMH Round Table. Anti- Mullerian hormone (AMH): what do we still need to know? Hum Reprod 2009; 24: 2264-75. [CrossRef]
59. Dólleman M, Faddy MJ, van Disseldorp J, van der Schouw YT, Messow CM, Leader B, et al. The relationship between anti-Müllerian hormone in women receiving fertility assessments and age at menopause in subfertile women: Evidence from large population studies. J Clin Endocrinol Metab 2013; 98: 1946-53. [CrossRef]
60. La Marca A, Sighinolfi1 G, Radi D, Argento C, Baraldi E, Artenisio AC, et al. Anti-Mullerian hormone (AMH) as a predictive marker in assisted reproductive technology (ART). Hum Reprod Update 2010; 16: 113-30. [CrossRef]
61. Broekmans FJ, Kwee J, Hendriks DJ, Mol BW, Lambalk CB. A systematic review of tests predicting ovarian reserve and IVF outcome. Hum Reprod Update 2006; 12: 685-718. [CrossRef]
62. Persani L, Rossetti R, Cacciatore C. Genes involved in human premature ovarian failure. J Mol Endocrinol 2010; 45: 257-79. [CrossRef]
63. Coulam CB, Adamson SC, Annegers JF. Incidence of premature ovarian failure. Obstet Gynecol 1986; 67: 604-6.
64. Anasti JN. Premature ovarian failure: An update. Fertil Steril 1998; 70: 1-15. [CrossRef]
65. van Kasteren YM, Schoemaker J. Premature ovarian failure: A systematic review on therapeutic interventions to restore ovarian function and achieve pregnancy. Hum Reprod Update 1999; 5: 483-92. [CrossRef]
66. Woad KJ, Watkins WJ, Prendergast D, Shelling AN. The genetic basis of premature ovarian failure. Aust N Z J Obstet Gynaecol 2006; 46: 242-4.[CrossRef]
67. Zinn AR, Tonk VS, Chen Z, Flejter WL, Gardner HA, Guerra R, et al. Evidence for a Turner syndrome locus or loci at Xp112-p221. Am J Hum Genet 1998; 63: 1757-66. [CrossRef]
68. Holland CM. 47,XXX in an adolescent with premature ovarian failure and autoimmune disease. J Paediatr Adolesc Gynecol 2001; 14: 77-80. [CrossRef]
69. Sherman SL. Premature ovarian failure in fragile X syndrome. Am J Med Genet 2000; 97: 189-94.[CrossRef]
70. Sullivan AK, Marcus M, Epstein MP, Allen EG, Anido AE, Paquin JJ, et al. Association of FMR1 repeat size with ovarian dysfunction. Hum Reprod 2005; 20: 402-12.[CrossRef]
71. Hundscheid RD, Sistermans EA, Thomas CM, Braat DD, Straatman H, Kiemeney LA, et al. Imprinting effect in premature ovarian failure confined to paternally inherited fragile X premutations. Am J Hum Genet 2000; 66: 413-8. [CrossRef]
72. Conway GS, Hettiarachchi S, Murray A, Jacobs PA. Fragile X premutaions in familial premature ovarian failure. Lancet 1995; 346: 309-10. [CrossRef]
73. Aittomäki K, Lucena JL, Pakarinen P, Sistonen P, Tapanainen J, Gromoll J, et al. Mutation in the follicle-stimulating hormone receptor gene causes hereditary hypergonadotropic ovarian failure. Cell 1995; 82: 959-68. [CrossRef]
74. Shelling AN, Burton KA, Chand AL, van Ee CC, France JT, Farquhar CM, et al. Inhibin: A candidate gene for premature ovarian failure. Hum Reprod 2000; 15: 2644-9. [CrossRef]
75. Shelling AN. X chromosome defects and premature ovarian failure. Aust N Z J Med 2000; 30: 5-7. [CrossRef]
76. Waggoner DD, Buist NR, Donnell GN. Long-term prognosis in galactosaemia: Results of a survey of 350 cases. J Inherit Metab Di 1990; 13: 802-18.[CrossRef]
77. De Baere E, Dixon MJ, Small KW, Jabs EW, Leroy BP, Devriendt K, et al. Spectrum of FOXL2 gene mutations in blepharophimosis-ptosis-epicanthus inversus (BPES) families demonstrates a genotype--phenotype correlation. Hum Mol Genet 2001; 10: 1591-600.[CrossRef]
78. Di Pasquale E, Beck-Peccoz P, Persani L. Hypergonadotropic ovarian failure associated with an inherited mutation of human bone morphogenetic protein-15 (BMP15) gene. Am J Hum Genet 2004; 75: 106-11. [CrossRef]
79. Laml T, Preyer O, Umek W, Hengstschlager M, Hanzal H. Genetic disorders in premature ovarian failure. Hum Reprod Update 2002; 8: 483-91. [CrossRef]
80. Bione S, Toniolo D. X chromosome genes and premature ovarian failure. Semin Reprod Med 2000; 18: 11-7. [CrossRef]
81. Biglieri EG, Herron MA, Brust N. 17-hydroxylation deficiency in man. J Clin Invest 1996; 45: 1946-54.[CrossRef]
82. La Barbera AR, Miller MM, Ober C, Rebar RW. Autoimmune etiology in premature ovarian failure. Am J Reprod Immunol Microbiol 1988; 16: 115-22.
83. Hoeck A, Schoemaker J, Drexhage HA. Premature ovarian failure and ovarian autoimmunity. Endocr Rev 1997; 18: 107-34. [CrossRef]
84. Bakalov VK, Vanderhoof VH, Bondy CA, Nelson LM. Adrenal antibodies detect asymptomatic autoimmune adrenal insufficiency in young women with spontaneous premature ovarian failure. Hum Reprod 2002; 17: 2096-100. [CrossRef]
85. Turkington RW, Lebovitz HE. Extra-adrenal endocrine deficiencies in Addison's disease. Am J Med 1967; 43: 499-507.[CrossRef]
86. Blumenfeld Z, Eckman A. Preservation of fertility and ovarian function and minimization of chemotherapy-induced gonadotoxicity in young women by GnRH-a. J Natl Cancer Inst Monogr 2005; 34: 40-3. [CrossRef]
87. Beerendonk CC, Braat DD. Present and future options for the preservation of fertility in female adolescents with cancer. Endocr Dev 2005; 8: 166-75. [CrossRef]
88. Morice P, Thiam-Ba R, Castaigne D, Haie-Meder C, Gerbaulet A, Pautier P, et al. Fertility results after ovarian transposition for pelvic malignancies treated by external irradiation or brachytherapy. Hum Reprod 1998; 13: 660-3. [CrossRef]
89. Nelson LM. Clinical practice. Primary ovarian insufficieny. N Eng J Med 2009; 306: 606-14. [CrossRef]
90. American College of Obstetricians and Gynecologists Committee on Genetics. ACOG committee opinion. No. 338: Screening for fragile X syndrome. Obstet Gynecol 2006; 107: 1483-5. [CrossRef]
91. Ataya KM, Rao LV, Lawrence E, Kimmel R. Luteinizing hormone-releasing hormone agonist inhibits cyclophosphamide-induced ovarian follicular depletion in rhesus monkeys. Biol Reprod 1995; 52: 365-72. [CrossRef]
92. Şükür YE, Özmen B, Sönmezer M. Cancer and ovarian tissue cryopreservation. Turk J Med Sci 2010; 40: 159-68.
93. Rebar RW, Connolly HV. Clinical features of young women with hypergonadotropic amenorrhea. Fertil Steril 1990; 53: 804-10.

Multiloculated cystic Mullerianosis of uterus: A case report

Pattomthadathil Sankaran Jayalakshmy, Shasi Velusamy, Joy Augustine
Department of Pathology, Government Medical College Thrissur, Kerala, India

Abstract

We are reporting a case of Mullerianosis, which presented as a multiloculated cystic mass on the serosal surface of the fundus of the uterus. Clinically and radiologically, this was interpreted as an ovarian tumor. Mullerianosis is a very rare benign tumor-like lesion. Awareness of this lesion is necessary to avoid misdiagnosis by clinicians, radiologists, and pathologists. (J Turk Ger Gynecol Assoc 2014; 15: 197-200)

Key words: Fundus of uterus, Mullerianosis, multiloculated cystic mass

Received: 01 January, 2013 **Accepted:** 25 January, 2014 **Available Online Date:** 08 August, 2014

Introduction

Mullerianosis was defined by Young and Clement (1) in 1996 as "a lesion seen at any site containing admixtures of endosalpingiosis, endometriosis, and endocervicosis -the three Mullerian glandular epithelia of tubal, endometrial, and endocervical type." For diagnosis of Mullerianosis, presence of an admixture of at least two types of Mullerian epithelium is necessary.

If only one type of epithelium is seen, the lesion is referred to as endometriosis, endosalpingiosis, or endocervicosis as per the type of lining cells present. Of these, endometriosis is a very common lesion and may be seen in any site, the most common site being the ovary. Endosalpingiosis and endocervicosis are rarer and have been reported mostly in the urinary bladder. Mullerianosis in which at least two types of Mullerian epithelium should be present is still rarer, and only a few cases have been reported in the English literature. Mullerianosis has been reported in sites, like the pelvic peritoneum, urinary bladder, ureter, and inguinal lymph node. But, Mullerianosis of the uterine fundus is very rarely reported.

Here, we report a case of Mullerianosis located in the fundus of the uterus presenting as a multiloculated cyst, clinically and radiologically mimicking an ovarian malignancy.

Case Presentation

A 48-year-old female presented with swelling in the lower abdomen. The clinical diagnosis was ovarian tumor. Imaging studies showed an ovarian mass. Total abdominal hysterectomy with bilateral salpingo-oophorectomy was done. The specimen received showed a uterus with both adenexae and a polypoid cystic mass attached to the fundus of the uterus. The uterus measured 8x5.5x2.5 cm. The cystic mass measured 9x8x9 cm. The cystic mass, on cutting open, showed a multiloculated cyst with locules of varying sizes filled with clear fluid. The wall was thin with a smooth inner surface. No solid areas were identified (Figure 1). Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A cut section of the uterus showed two intramural fibroids, the larger one measuring 1 cm at the greatest diameter. The endometrium, endocervix, and ectocervix were unremarkable. The left ovary measured 3x1.5x1 cm and showed a cyst attached to one pole measuring (m/s) 3 cm at the greatest diameter, which on opening showed a thin-walled uniloculated cyst filled with clear fluid. The right ovary and both fallopian tubes were grossly unremarkable.

Microscopic examination of the fundal cyst showed a multiloculated cyst with microcystic spaces. The locules of the cysts were lined by variable types of epithelium, the predominant being ciliated columnar epithelium of the tubal type (Figure 2). Some of the locules were lined by flat to cuboidal epithelium (Figure 3). Focal areas showed closely packed glandular structures with stratification of the lining epithelium (Figure 4). Cellular atypia was not found in these areas. No mitotic activity was seen; the low proliferative nature was confirmed by Ki67 immunostaining. The cystic spaces were filled with eosinophilic secretion with neutrophil infiltrate in some spaces. Focally, endometrial-type small glandular structures were seen (Figure 5). The stroma was also variable in nature. It was myomatous, fibrous, and myofibromatous in areas (Figure 5, 6). Multicystic mesothelioma was a differential diagnosis grossly and histologically. The calretinin immunostaining was negative in the glandular lining cells, which ruled out this differential diagnosis.

Address for Correspondence: *Pattomthadathil Sankaran Jayalakshmy, Department of Pathology, Government Medical Colleges Thrissur, Kerala, India. Phone: 944 761 52 94 e.mail: psjayalakshmy@gmail.com*

DOI:10.5152/jtgga.2014.76736

Figure 1. Cut section of uterus showing multiloculated cystic mass attached to the serosa of the fundus

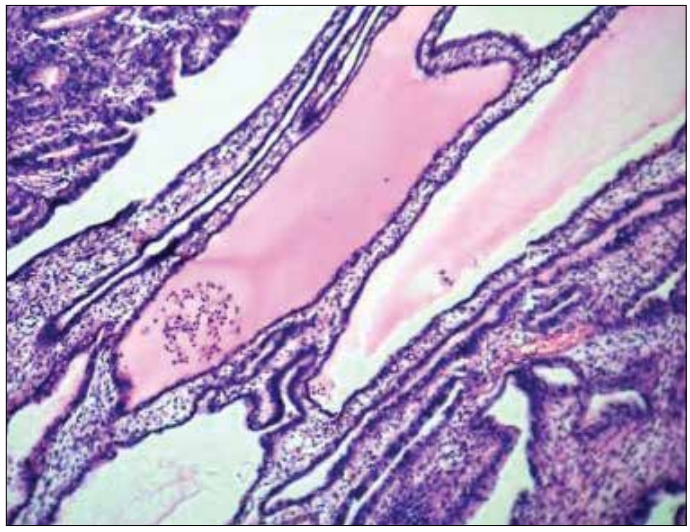

Figure 3. Locules of the cyst lined by flat to low cuboidal epithelium. Lumen shows eosinophilic secretion and neutrophil collection (H&E x100)

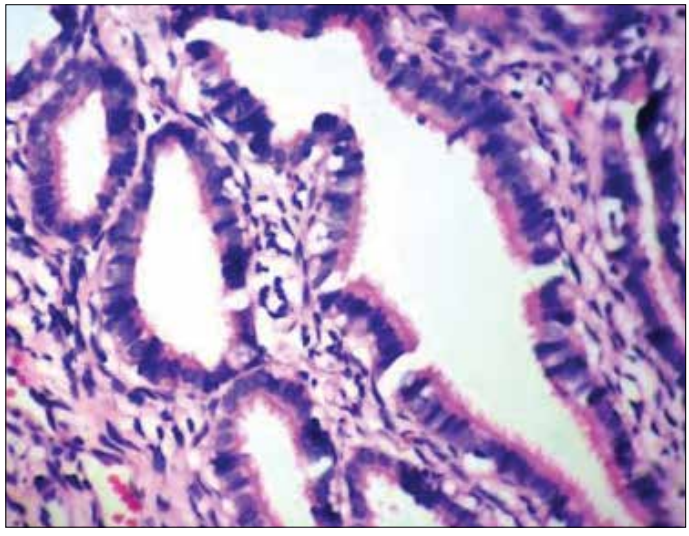

Figure 2. Locules and glandular spaces lined by ciliated tall columnar epithelium of tubal type (H&E x400)

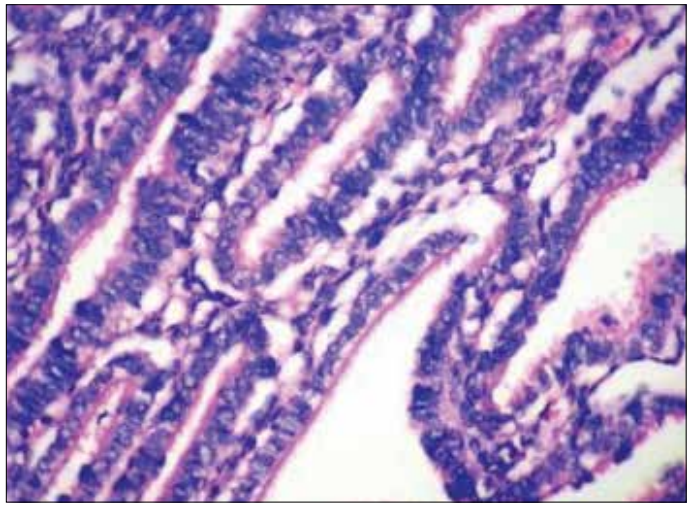

Figure 4. Crowed glandular structures showing stratification of nuclei (H&E x400)

The uterus showed 2 small intramural leiomyomas, proliferative endometrium, and chronic cervicitis. The left ovary showed a simple serous cyst. The right ovary and both fallopian tubes were histologically unremarkable.

Immunohistochemistry for cytokeratin (CK) was strongly positive in the lining cells. Calretinin was negative. Ki-67 showed no proliferative activity in the glandular epithelium (Figure 7).

Discussion

Mullerianosis was defined by Young and Clement in 1996 as a lesion seen at any site containing Mullerian glandular epithelia of tubal, endocervical, and endometrial type (1). At least any two of the Mullerian tissues should be present for the diagnosis of Mullerianosis. Mullerianosis was considered a choristoma of the Mullerian rest (2). This is a benign tumor-like lesion and has been reported in the urinary bladder, mesosalpinx, pelvic peritoneum, and inguinal lymph nodes (3-5).

If only the tubal-type epithelium is present in the lesion, the condition is termed endosalpingiosis. Endosalpingiosis was first described by Sampson in 1930 (6).

Endosalpingiosis is usually an incidental finding. But, sometimes, it may present as a tumorous mass. Clement and Young described four cases of florid cystic endosalpingiosis presenting as a tumor-like mass (7). The fifth case of florid endosalpingiosis had been reported in the uterine fundus as a multiloculated cystic mass (8), grossly similar to our case. But, histologically, only endosalpingiotic tissue was present and lacked the endometrial-type glands, as seen in the present case. In the case of florid cystic endosalpingiosis reported by M Heatley et al. (9), there were multiple small cysts in the uterus extending into the parametrium and broad ligament. Batt et al. (2) suggested that for the diagnosis of Mullerianosis, the following criteria

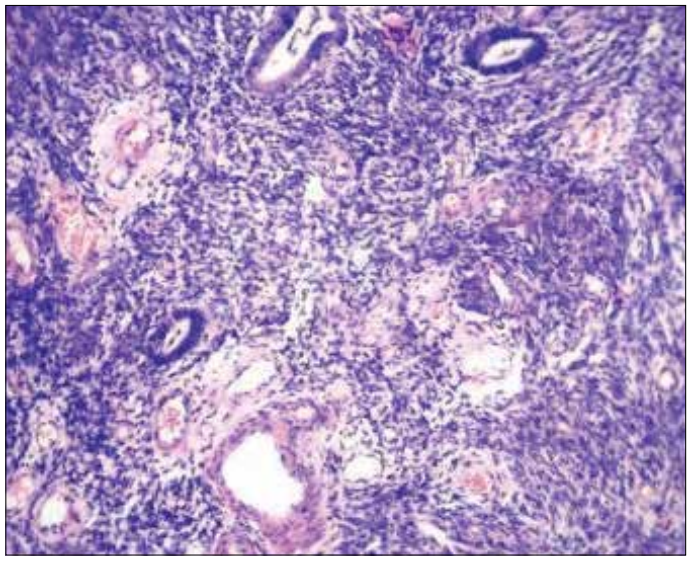

Figure 5. Endometrial type glands in a fibrous stroma with prominent hyalinized vessels (H&E x100)

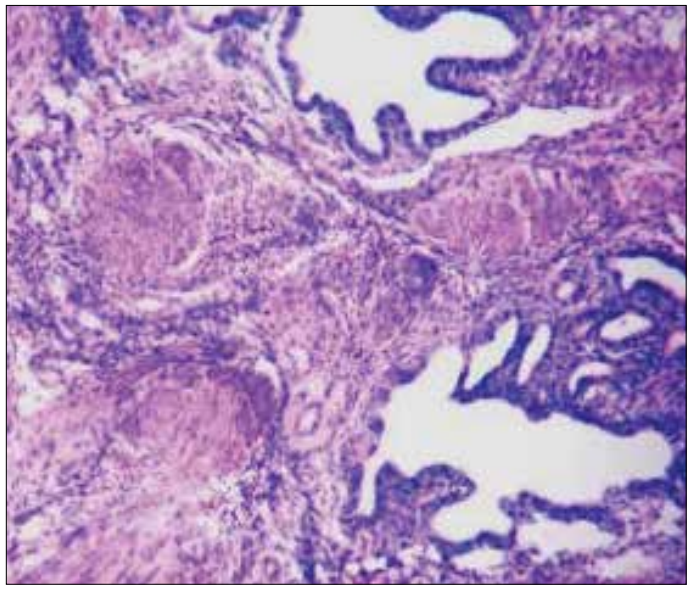

Figure 6. Smooth muscle stroma (H&E x100)

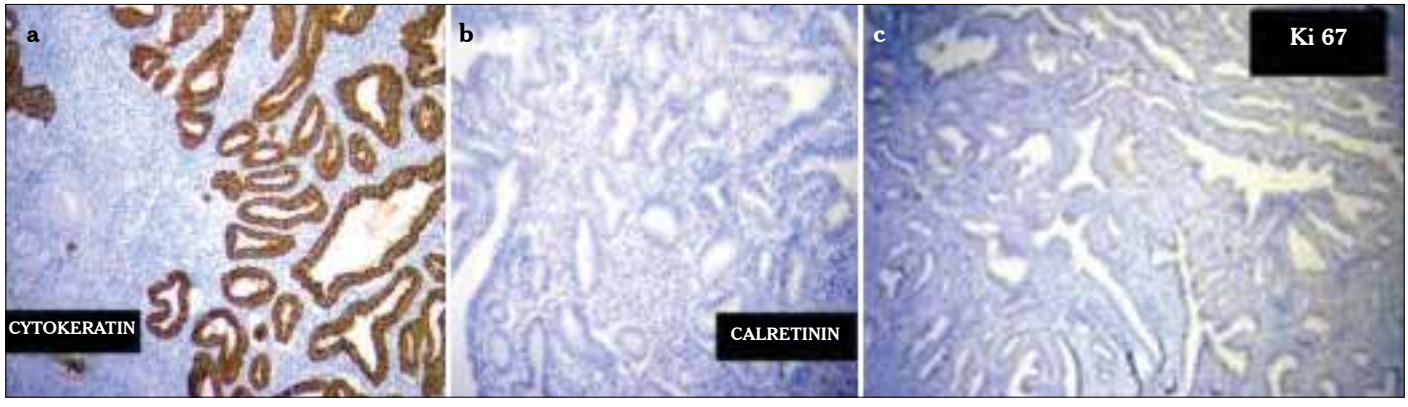

Figure 7. a-c. Immunostains (x100) showing cytokeratin positivity in the glandular epithelial cells (a). Calretinin is negative, ruling out mesothelial cyst (b). Ki-67 shows low proliferative index, ruling out an adenocarcinoma (c)

should be met: the patient should have no evidence of pelvic endometriosis; no history of surgery to the reproductive organs; and no direct communication of the lesion with the endocervix, endometrium, or endosalpinx. In our case, all these criteria were satisfied.

The pathogenesis of this lesion is still in debate. A developmental theory (2), an implantation theory (10), and a metaplastic theory (11) have been put forward. In our case, the patient was a middle-aged female, and no associated developmental anomalies were seen to propose a developmental theory. The metaplastic theory seems to be more appropriate in this case. The tumor might have originated from the serosal (peritoneal) covering of the uterine fundus, probably by a metaplastic conversion of the mesothelial cells to Mullerian epithelium.

The clinical importance of this lesion is that it must be distinguished from malignancy, because the glandular structures and cell/nuclear stratification may resemble an adenocarcinoma. Mullerianosis is a benign lesion having no invasion to the deeper tissue, whereas adenocarcinoma is invasive to the adjacent tissue. Adenocarcinomas show cellular features of malignancy and high proliferative index. In our case, no invasion to the adjacent fundal myometrium was seen. Though there were some focal glandular crowding and nuclear stratification, mitotic activity was not seen. Ki-67 immunostaining showed no proliferative activity. This lesion is also a close mimicker of mesothelioma, which may present as a multiloculated cystic mass and may be seen attached to the uterine serosal surface. But, microscopically, the tubal- and endometrial-type epithelium is characteristic of Mullerianosis. Moreover, in our case, calretinin immunostaining was negative, ruling out mesothelioma

To conclude, Mullerianosis is a very rare benign tumor-like lesion. The fundus of the uterus is a rare site, and the previously reported sites have been the pelvic peritoneum, urinary bladder, mesosalpinx, and inguinal lymph nodes. Awareness of this rare lesion is helpful for the clinician and radiologists to avoid a misdiagnosis of ovarian tumor. Pathologists should not misdiagnose this lesion as a malignancy and should differentiate it from adenocarcinoma and mesothelioma with appropriate immunostaining if the morphological diagnosis is difficult.

Ethics Committee Approval: *N/A.*

Informed Consent: *Written informed consent was obtained from patient who participated in this case.*

Peer-review: *Externally peer-reviewed.*

Author contributions: *Concept - P.S.J., J.A.; Design - P.S.J., J.A.; Supervision - P.S.J., J.A .; Resource - P.S.J., V.S.; Materials - P.S.J., V.S.; Data Collection&/or Processing - P.S.J., V.S.; Analysis&/or Interpretation - P.S.J., V.S.; Literature Search - P.S.J., V.S .; Writing - P.S.J.; Critical Reviews - J.A., V.S.*

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

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

References

1. Young RH, Clement PB. Mullerianosis of the urinary bladder. Mod Pathol 1996; 9: 731-7.
2. Batt RE, Smith RA, Buck Louis GM, Martin DC, Chapron C, Koninckx PR, Yeh J. Müllerianosis. Histol Histopathol 2007; 22: 1161-6.
3. Lim S, Kim JY, Park K, Kim BR, Ahn G. Mullerianosis of the mesosalpinx: a case report. Int J Gynecol Pathol 2003; 22: 209-212. [CrossRef]
4. Young RH, Clement PB. Mullerianosis of the urinary bladder. Mod Pathol 1996; 9: 731-7.
5. Sinkre P, Hoang MP, Albores-Saavedra J. Mullerianosis of inguinal lymph nodes: Report of a case. Int J Gynecol Pathol 2002; 21: 60-4. [CrossRef]
6. Simpson JA. Postsalpingectomy endometriosis, (endosalpingiosis). Am J Obstet Gynecol 1930; 20: 443-80.
7. Clement PB, Young RH. Florid cystic endosalpingiosis with tumor-like manifestations: a report of four cases including the first reported cases of transmural endosalpingiosis of the uterus. Am J Surg Pathol 1999; 23: 166-75. [CrossRef]
8. Kajo K, Zúbor P, Macháleková K, Plank L, Visnovský J. Tumor-like manifestation of endosalpingiosis in uterus: A case report. Pathol Res Pract 2005; 201: 527-30. [CrossRef]
9. Heatley MK, Russell P. Florid cystic endosalpingiosis of the uterus. J Clin Pathol 2001; 54: 399-400. [CrossRef]
10. Maniar KP, Kalir TL, Palese MA, Unger PD. Endosalpingiosis of the urinary bladder:a case of probable implantative origin with characterization of benign Fallopian tube immunohistochemistry. Int J Surg Pathol 2010; 18: 381-3.
11. Lauchlan, Stuart C. The secondary Müllerian system. Obstet Gynecol Surv 1972; 27: 133-46. [CrossRef]

Persistent ascites due to sclerosing encapsulating peritonitis mimicking ovarian carcinoma: A case report

Mete Çağlar[1], Nilüfer Çetinkaya[2], Emre Özgü[2], Tayfun Güngör[2]

[1]Department of Obstetrics and Gynecology, Düzce University Faculty of Medicine, Düzce, Turkey

[2]Department of Gynecologic Oncology, Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara, Turkey

Abstract

Sclerosing encapsulating peritonitis, also known as '*Cocoon Syndrome*', is a rare cause of bowel obstruction. The condition might be congenital or acquired and has non-specific symptomatology. Abdominal pain occurs due to the limitation of intestinal motility or segment obstruction by a thick homogenous fibrotic mantle covering the intra-peritoneal organs. Altered peritoneal fluid dynamics result in persistent ascites. Leading pathogenic theories are not well defined, but genetic factors, retrograde trans-tubal flow of causative agents, peritoneal infections, medications and peritoneal invasive procedures are all thought to play a role. There are no specific diagnostic criteria and exact diagnosis is only confirmed during surgery when the investing thick fibrous folds covering the bowel loops are visualised. We present here a case that had been suspected to have an ovarian malignancy due to a huge abdominal heterogeneous mass and ascites on preoperative diagnostic workup, but had a final diagnosis of abdominal *Cocoon Syndrome* made during surgery. (J Turk Ger Gynecol Assoc 2014; 15: 201-3)

Key words: Abdominal *Cocoon Syndrome*, sclerosing encapsulating peritonitis, ascites

Received: 08 August, 2013 **Accepted:** 02 November, 2013 **Available Online Date:** 08 August, 2014

Introduction

'*Abdominal Cocoon Syndrome*' is characterised by the presence of thick homogenous fibrotic mantle covering the intra-peritoneal organs. The condition can be either congenital or acquired. There is no specific symptomatology related with the disease. The exact cause has not been well studied, but genetic factors, trans-tubal flow of causative agents, peritoneal infections, medications and peritoneal invasive procedures are all thought to play a role (1).

Encapsulating membrane in abdominal Cocoon Syndrome is composed of dense fibrotic tissue and has no mesothelial cell covering (2). Cocoon Syndrome causes the disordered peritoneal fluid dynamics due to restricted bowel movements and the presence of a thick fibrous mantle surrounding the intestinal loops. These factors lower the trans-mural lymph flow and result in persistent ascites.

Case Presentation

A thirty-six year old, gravida 1, parity 1 female was admitted to a gynaecology clinic one year previously due to secondary infertility. She had no chronic illnesses in her past medical history. She gave birth six years ago by caesarean section after spontaneous pregnancy. Upon admission, she had menstrual regularity and hormonal evaluation was within normal limits. On trans-vaginal ultrasonography she had a normal appearing uterus and adnexa with ascites in the pouch of Douglas. Trans-abdominal ultrasonography revealed grade I hepatosteatosis and abdominal ascites that was measured as 8 cm at the deepest point with free fluid accumulation surrounding the bladder and in between the bowel loops. Tumour markers including carcinoembryonic antigen (CEA), CA 125, CA 19-9, CA 15-3 and alpha fetoprotein (AFP) were normal and the patient was sent to the gastroenterology department for a differential diagnosis for ascites. She had normal liver function tests and albumin levels upon admission. Colour Doppler evaluations of the portal venous system and inferior vena cava were performed. On Doppler sonography, portal venous branches, splenic vein, inferior vena cava and hepatic veins had normal calibres and flow patterns. Also, the presence of luminal thrombi was excluded. Liver architecture was normal with no suspicious lesions and ascites was measured as 12 cm at its deepest point. Paracentesis revealed the presence of lymphocytic, histiocytic cells and mesothelial proliferation without atypia. Gastrointestinal malignancy was excluded due to these investigations. The patient was advised to return for re-evaluation after 3 months. However, the patient did not return for the follow-up.

The same patient was then admitted to our clinic one year later with the desire to become pregnant. She described pelvic pain during menses for 3 months. Her Pap test and hormonal profile were normal. During transvaginal ultrasonography, a 20x18 cm abdominal heterogeneous solid-cystic mass undifferentiated from the left adnexa with ascites was diagnosed. Tumour markers were normal. The patient was

Address for Correspondence: *Nilüfer Çetinkaya, Department of Gynecologic Oncology, Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara, Turkey. Phone: +90 533 203 84 49 e.mail: cetinkayanilufer@gmail.com*

DOI:10.5152/jtgga.2014.37268

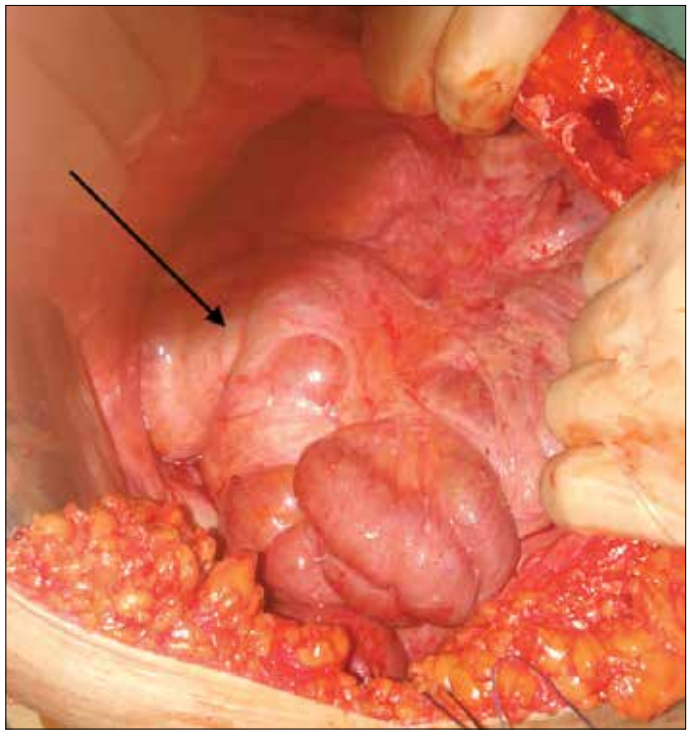

Figure 1. Arrow shows the thick fibrous mantle surrounding the bowel loops. Liver, stomach and spleen are also located within this fibrous capsule

prepared for diagnostic laparotomy with the probability of ovarian carcinoma due to new onset pelvic pain, a huge abdominal mass and ascites.

During the operation, about 2500 mL clear ascites was removed after peritoneal entry and thick fibrotic tissue encapsulating the abdominal organs including the liver, stomach, spleen, but excluding the uterus and adnexa, was observed (Figure 1). There was also an 8 cm, benign cyst on the left ovary. The diagnosis of sclerosing encapsulating peritonitis was made during surgery and the operation was terminated following left ovarian cystectomy with the absence of malignancy on frozen section.

The patient was discharged from the hospital on the third postoperative day without any complications. The permanent pathology result was reported one week later as a benign ovarian serous cyst. The patient was scheduled for evaluation in the infertility clinic 3 months after surgery and written informed consent was obtained from the patient to present her medical history in this study.

Discussion

Peritoneal fluid dynamic depends on diaphragmatic lymph flow and desired effects of bowel movements. Peritoneal fluid drains primarily to the upper abdominal, diaphragmatic lymph nodes and then continues via the thoracic duct to the mediastinum (3).

Diaphragmatic movements during inspiration and expiration, bowel peristalsis and impacts of abdominal wall musculature affect the peritoneal fluid dynamics. Blood and lymphatic vessels along the bowel wall also affect the absorption of peritoneal fluid with their hydrostatic and oncotic pressures.

Portal hypertension due to cirrhosis, hepatic congestion or portal thrombus formation is the primary cause of ascites. Hypoalbuminaemia, which leads to decreased plasma oncotic pressure, is also an important issue in the aetiology of ascites. Furthermore, peritoneal disease, medical disorders and malignant conditions are known to be associated with ascites. Intractable ascites is a term that reflects the presence of ascites in spite of strict sodium restriction and the maximal diuretic dose of furosemide and spironolactone (4).

Abdominal Cocoon Syndrome frequently presents with vague abdominal symptoms that do not clearly indicate a known aetiology. Bowel obstruction, abdominal mass, ascites and abdominal pain are the most common clinical presentations related with this syndrome.

Most of the patients are known to have symptoms associated with peritoneal tuberculosis, peritoneal dialysis, sarcoidosis, systemic lupus erythematosus, β-blocker use, cirrhosis and ventriculoperitoneal shunts (5). Patients are usually diagnosed per-operatively but procedures like ultrasonography or computed tomography (CT) have preoperative diagnostic roles. CT is known to be the gold standard diagnostic work-up due to the ease and feasibility of luminal assessment (1). Oral contrast studies might also present bowel obstructions which facilitate therapeutic interventions (6).

In patients with bowel obstruction, the goal of treatment consists of resection of fibrous coverage and lysis of adhesions between the bowel loops to free the entire gut (7). Bowel resection is rarely indicated and necessary in the presence of highly oedematous, obstructive or necrotic segments.

In our patient, we did not see any symptoms pointing to the bowel obstruction preoperatively. The diagnosis of abdominal mass and persistent ascites for a period longer than a year in the presence of new onset pelvic pain was the main indication for surgery. The diagnosis of Cocoon Syndrome was made at the time of surgery when the ascites was drained. Lysis of the fibrous mantle was not performed in our case due to the absence of any bowel obstruction.

This case report represents a rare abdominal Cocoon Syndrome with persistent ascites and an accompanying left ovarian serous cyst. Our aim is to ensure that clinicians keep this rare condition in mind when faced with the presence of persistent ascites without any concomitant organ pathologies. Also, preoperative findings might indicate this syndrome, perhaps via a mixture of large cystic and solid masses with different degrees of swinging features in its core during ultrasonography. To date, the differential diagnosis of this condition consists of the exclusion of other aetiologies with ascites and measurements of tumour markers to reject probable malignant diseases. Females with abdominopelvic pain, ascites and an adnexal mass that is suspicious of ovarian malignancy, especially in the presence of negative tumour markers, might require attention in gynaecology clinics for the differential diagnosis of abdominal Cocoon Syndrome.

Ethics Committee Approval: *Ethics committee approval was received for this study.*

Informed Consent: *Written informed consent was obtained from patient who participated in this study.*

Peer-review: *Externally peer-reviewed.*

Author contributions: *Concept - M.C., N.C., E.O., T.G.; Design - M.C., N.C., E.O., T.G.; Supervision M.C., N.C., E.O., T.G.; Resource - M.C., N.C., E.O., T.G.; Materials - M.C., N.C., E.O., T.G.; Data Collection&/or Processing - M.C., N.C., E.O., T.G.; Analysis&/or Interpretation - M.C., N.C., E.O., T.G.; Literature Search - M.C., N.C., E.O., T.G.; Writing - M.C., N.C., E.O., T.G.; Critical Reviews - M.C., N.C., E.O., T.G.*

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

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

References

1. Solak A, Solak İ. Abdominal cocoon syndrome: Preoperative diagnostic criteria, good clinical outcome with medical treatment and review of the literature. Turk J Gastroenterol 2012; 23: 776-9.
2. Yeniay L, Karaca CA, Calışkan C, Fırat O, Ersin SM, Akgün E. Abdominal cocoon syndrome as a rare cause of mechanical bowel obstruction: Report of two cases. Ulus Travma Acil Cerrahi Derg 2011; 17: 557-60. **[CrossRef]**
3. Parungo CP, Soybel DI, Colson YL, Kim SW, Ohnishi S, DeGrand AM, et al. Lymphatic drainage of the peritoneal space: a pattern dependent on bowel lymphatics. Ann Surg Oncol 2007; 14: 286-98. **[CrossRef]**
4. Zervos EE, Rosemurgy AS. Management of medically refractory ascites. Am J Surg 2001; 181: 256-64. **[CrossRef]**
5. Singh B, Gupta S. Abdominal cocoon: A case series. Int J Surg 2013;11: 325-8. **[CrossRef]**
6. Wei B, Wei HB, Guo WP, Zheng ZH, Huang Y, Hu BG, Huang JL. Diagnosis and treatment of abdominal cocoon: a report of 24 cases. Am J Surg 2009; 198: 348-53. **[CrossRef]**
7. Chew MH, Sophian Hadi I, Chan G, Ong HS, Wong WK. A problem encapsulated: the rare peritoneal encapsulation syndrome. Singapore Med J 2006; 47: 808-10.

What is your diagnosis?

A patient who was 30 years old was referred to our clinic at the 16th week of gestation. It was her first IVF pregnancy. Ultrasonographic examination showed an anechoic image that measured 80x59 mm (Figure 1). What is your diagnosis?

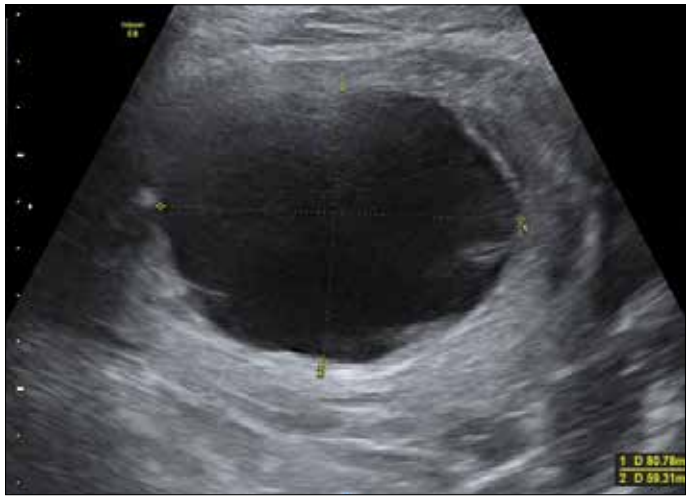

Figure 1. Cystic mass in the uterine cavity

Address for Correspondence: *Halis Özdemir, Department of Obstetrics and Gynecology, Adana Başkent University Hospital, Adana, Turkey.*
Phone: +90 505 934 42 15 e.mail: drhalisozdemir@gmail.com

DOI:10.5152/jtgga.2014.0005

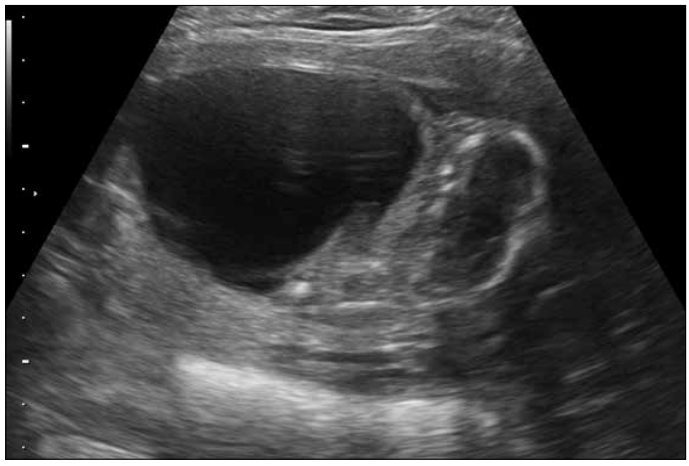

Figure 2. Fetal part and megacystis

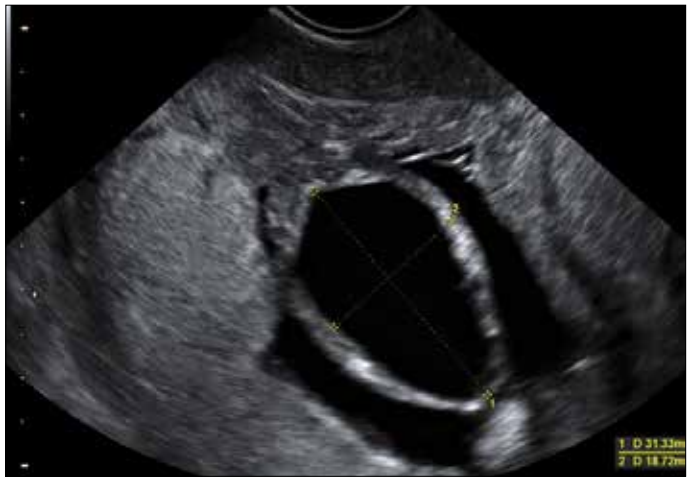

Figure 3. Bladder measured 31x18 mm at twelfth week of gestation

Answer

Ultrasound examination revealed a fetal part near the anechoic cyst. We realized a calvarium and that the fetal heart was not beating (Figure 2). A previous ultrasonographic image at 12 weeks of pregnancy showed that the fetal bladder was 31x18 mm length and showed hyperechogenic kidneys (Figure 3).

This case was related with fetal megacystis. Megacystis is an anomaly that is visible at any week of gestation. The incidence of this anomaly is not known. Megacystis is the longitudinal size of a fetal bladder greater than 7 mm in the first trimester (1). The most common cause of megacystis is lower urinary tract obstruction (2). Megacystis can also be associated with chromosomal anomalies (mostly with trisomy 13 and 18) (3). Genetic examination should be done in the cases of megacystis. Urethral atresia, posterior urethral valve, megalourethra, prune belly syndrome, and megacystis-microcolon-intestinal hypoperistalsis syndrome can be other reasons of megacystis. The definition of megacystis in the second and third trimester is more subjective than the first trimester.

Enlarged bladder in 45 minutes during an examination can be used to diagnose for megacystis in the second and third trimester (1). In the second and third trimester, lower urinary tract obstruction (LUTO) frequently can be caused by posterior urethral valve

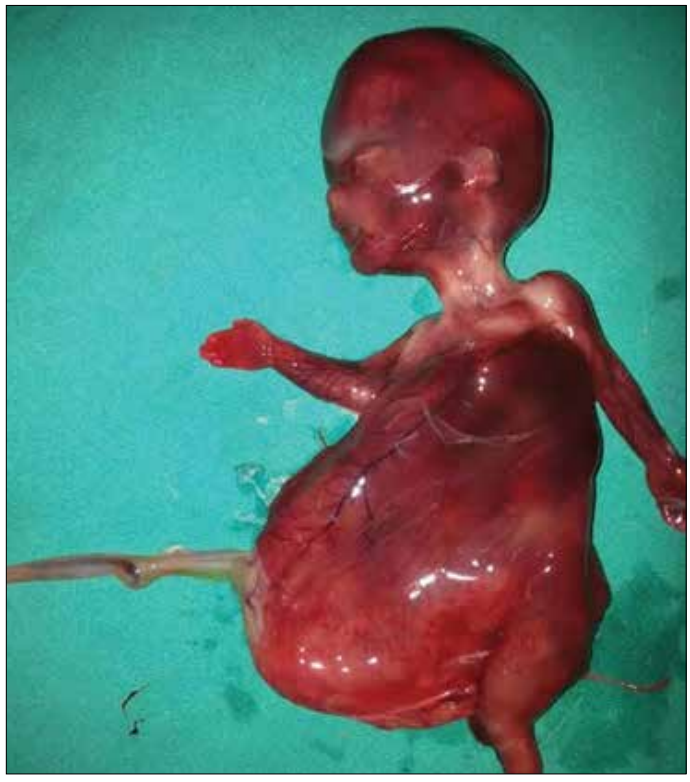

Figure 4. The fetus after termination of pregnancy

(PUV) in male fetuses with megacystis. Keyhole sign in sonographic examination is important for the diagnosis of PUV (4).

Survival of fetuses with megacystis in the second and third trimester is better than in the first trimester (1). Bladder drainage not only reduces the risk of pulmonary hypoplasia but also increases survival. Vesicocentesis and vesico-amniotic shunting may be used for the drainage of bladder (1).

In our case, the patient was offered chorionic villus sampling and termination of the pregnancy when we diagnosed megacystis, oligohydroamnios, and bilateral renal dysplasia in the first trimester. But, the family did not accept. We observed the fetus with a megacystis 80 mm wide and no heart beating 4 weeks later. After informed consent, we terminated the pregnancy (Figure 4).

Didem Alkaş, Halis Özdemir, Hakan Kalaycı, Tayfun Çok, Ebru Tarım
Department of Obstetrics and Gynecology, Adana Başkent University Hospital, Adana, Turkey

References

1. Bornes M, Spaggiari E, Schmitz T, Dreux S, Czerkiewicz I, Delezoide AL, et al. Outcome and etiologies of fetal megacystis according to the gestational age at diagnosis. Prenat Diagn 2013; 33: 1162-6. [CrossRef]
2. Confer SD, Galati V, Frimberger D, Kropp BP. Megacystis with an anterior urethral valve: Case report and review of literature. J Pediatr Urol 2010; 6: 459-62. [CrossRef]
3. Osborne NG, Bonilla-Musoles F, Machado LE, Raga F, Bonilla F Jr, Ruiz F, et al. Fetal megacystis: differential diagnosis. J Ultrasound Med 2011; 30: 833-41.
4. Machado, Matias A, Rodrigues M, Mariz C, Monteiro J, Montenegro N. Fetal megacystis as a prenatal challenge: megacystis-microcolon-intestinal hypoperistalsis syndrome in a male fetus. Ultrasound Obstet Gynecol 2013; 41: 345-7. [CrossRef]

Domestic violence against pregnant women: A prospective study in a metropolitan city, İstanbul

Dear Editor,

We read with interest the article by Cengiz H. et al. (1), published in the June 2014 issue of the *Journal*. The authors report their survey data on pregnant women interviewed for physical and sexual violence attending their institution's antenatal outpatient clinics. They report a 2.4% frequency of physical and/or sexual abuse during pregnancy. The study includes over 1300 pregnant women and clearly aids to increase awareness of the "domestic violence problem" against pregnant women in Turkey among obstetricians and gynecologists. However, we believe that the figure they report (2.4%) is an underestimate.

First, this was not a population-based study. No sampling was performed, either. Therefore, the data suffer from sampling bias. Women were simply interviewed by a clinic nurse in so-called "complete privacy" at the hospital setting. The authors also state that "pregnant women were afraid to disclose their experiences." This is not surprising, as the authors were not able to provide suitable circumstances while interviewing the women on such a sensitive issue.

Second, the survey seems to include certain questions merely on physical and sexual violence. Nevertheless, domestic violence apparently incorporates many additional behaviors: (a) *any physical violence* causing actual bodily harm, from pushing, jolting, manhandling, dashing, kicking, and scragging to stabbing and shooting; (b) *sexual assault* in an unacceptable manner, place, and time and sexual abuse, including any other act of sexual violence; (c) *economic violence* to control a woman's income and/or employment and other acts to prevent the economic freedom of the female partner; (d) *emotional abuse*, including bullying, creating fear, blackmailing, and controlling behaviors, such as isolation of the woman from her family of birth, friends, or social life, and forcing her to stay at, or leave, the home; and (e) *psychological or verbal abuse,* including acts, such as insulting, making fun of personal weaknesses, using humiliating nicknames, and shouting (2-4). Hence, the present data do not reflect many forms of domestic violence, such as economic and emotional abuse. Moreover, the definition of sexual violence in the present study was limited, seemingly restricted to forced sexual intercourse (nonconsensual sexual activity). In fact, sexual violence against a woman is a broader term that includes "any sexual act, attempt to obtain a sexual act, unwanted sexual comments, or advances directed against the woman's sexuality" (5). If the authors had questioned all of these categories appropriately, the frequency of domestic violence should have been much higher than 2.4%.

Third, there is a potential bias concerning the timing of data collection. The surveys were performed during clinical antenatal visits. Hence, women at various gestational ages were probably included. For example, data from the first, second, and third trimesters seem to be pooled. This may also lead to an underestimated prevalence, since such a design will miss women surveyed during early pregnancy who will subsequently be exposed to domestic violence. Therefore, a more suitable design would be to interview women throughout the peripartum period, for example, during early puerperium.

In conclusion, we suppose that the relatively low prevalence of physical and sexual abuse against pregnant women reported by Cengiz et al. (1) do not reflect the actual figures in their population, in Istanbul or in Turkey, due to critical limitations of the study.

Mekin Sezik[1], Yonca Sönmez[2]
[1]Department of Obstetrics and Gynecology, Süleyman Demirel University Faculty of Medicine, Isparta, Turkey
[2]Department of Public Health, Süleyman Demirel University Faculty of Medicine, Isparta, Turkey

References

1. Cengiz H, Kanawati A, Yıldız S, Süzen S, Tombul T. Domestic violence against pregnant women: A prospective study in a metropolitan city, İstanbul. J Turk Ger Gynecol Assoc 2014; 15: 74-7.
2. Pallitto CC, García-Moreno C, Jansen HA, Heise L, Ellsberg M, Watts C; WHO Multi Country Study on Women's Health and Domestic Violence. Intimate partner violence, abortion, and unintended pregnancy: results from the WHO Multi-country Study on Women's Health and Domestic Violence. Int J Gynaecol Obstet 2013; 120: 3-9.
3. İzmirli GO, Sönmez Y. Isparta ili Gönen ilçesinde yaşayan 15-49 yaş grubu evli kadınların aile içi şiddete maruz kalma sıklığı ve aile içi şiddet görmeye sebep olan faktörler. Postgraduate Dissertation, Süleyman Demirel University, 2013.
4. İzmirli GO, Sonmez Y, Sezik M. Prediction of domestic violence against married women in southwestern Turkey. Int J Gynaecol Obstet 2014; pii: S0020-7292(14)00374-9. doi: 10.1016/j.ijgo.2014.06.011. [Epub ahead of print]
5. World Health Organization. World report on violence and health. Geneva: World Health Organization. 2002: 17-18.

Address for Correspondence: *Mekin Sezik, Department of Obstetrics and Gynecology, Süleyman Demirel University Faculty of Medicine, Isparta, Turkey. Phone: +90 246 211 9239 e.mail: msezik@yahoo.com*

DOI:10.5152/jtgga.2014.13148

Author's Response

We appreciate and thank the authors for their comments on our study. We reconsidered the main points of the study regarding the evaluation of the authors. Firstly, we tried to conduct a cross-sectional study. However, we totally agree with the authors on what they criticized about the timing bias. The study could be designed according to the gestational age of the pregnant women who participated in our study. Due to privacy issues and the interview technique, we can say that the hospital circumstances, such as lack of private rooms, were not perfectly proper to collect 100% accurate information about domestic violence from the participants. In addition, we also were surprised about the result of the percentage of women who had experienced domestic violence. We observed similar results in terms of domestic violence among pregnant women, such as 4.67% from the study published by Ergonen et al. (1). Nevertheless, the questionnaire of our study focused on physical, sexual, and verbal abuse. It is a fact that the investigation about other types of violence will increase the rate of violence in pregnancy (2). We want to thank the authors once again for highlighting this important subject. In this study, our aim was to increase the awareness of health care providers about domestic violence against pregnant women.

Hüseyin Cengiz
Department of Obstetrics and Gynecology, Bakırköy Dr. Sadi Konuk Training and Research Hospital, İstanbul, Turkey

References

1. Ergönen AT, Ozdemir MH, Can IO, Sönmez E, Salaçin S, Berberoğlu E, Demir N. Domestic violence on pregnant women in Turkey. J Forensic Leg Med 2009; 16: 125-9. [CrossRef]
2. Johnson JK, Haider F, Ellis K, Hay DM, Lindow SW. The prevalance of domestic violence aganist pregnant women. BJOG 2003; 110: 272-5. [CrossRef]

CONGRESS CALENDAR

INTERNATIONAL MEETINGS

9-12 October, 2014	**11th Congress of the Mediterranean Association for Ultrasound in Obstetrics and Gynecology** Antalya, Turkey www.perinatal.org.tr
17-21 November, 2014	**43rd AAGL Global Congress on Minimally Invasive Gynecology** Vancouver, Canada http://www.aagl.org/globalcongress/
20-22 November, 2014	**20th Asia Pasific COGI 6th Asia Pacific Congress on Controversies in Gynecology, Infertility & Ultrasound (COGI)** Saigon, Vietnam www.cogi.org
4-7 December, 2014	**20th World Congress on Controversies in Obstetrics, Gynecology & Infertility (COGI)** Paris, France www.cogi.org
11-12 December, 2014	**6th Annual Seminar on Minimally Invasive & Robotic Gynecologic Surgery** New York, USA www.cogi.org
8-12 April, 2015	**3rd Annual Middle East Society for Gynecologic Endoscopy (MESGE) Congress & 6th Annual Congress of Turkish Society of Gynecological Endoscopy (TSGE) Conjoint Meeting** Antalya, Turkey www.mesge2015.org
11-13 June, 2015	**7th SERG Meeting** İstanbul, Turkey www.sergs2015.org
16-19 June, 2015	**11th AAGL International Congress on Minimally Invasive Gynecology & 15th Annual Meeting of the Israeli Society of Gynecologic Endoscopy - ISGE IL Conjoint Meeting** Jerusalem, Israel www.aagljerusalem2015.com

NATIONAL MEETINGS

24-27 September, 2014	**9th National Maternal-Fetal Medicine and Perinatology Congress** İstanbul, Turkey http://www.tmftpkongre2014.org/en/
15-18 October, 2014	**7th National Urogynecology Congress** İstanbul, Turkey http://urojinekoloji2014.org/
6-9 November, 2014	**6th Biannual Meeting of the Turkish Society of Reproductive Medicine** Antalya, Turkey http://2014.tsrm.org.tr/
19-23 November, 2014	**14th National Gynecologic Oncology Congress** Antalya, Turkey www.trsgo.org

JTGGA CME/CPD CREDITING

Questions on the article titled *"Ovarian cystectomy in endometriomas: Combined approach"* within the scope of CME/CPD

1. What is the cutoff value of HE4 (human epididymis secretory protein 4) for discriminating ovarian epithelial cancers from endometriomas?
   a) 5 pM
   b) 35 pM
   c) 40 pM
   d) 70 pM
   e) 170 pM

2. Which cancers are related to endometrioma?
   a) 40% of endometrioid ovarian carcinomas and 50% of clear-cell ovarian carcinomas
   b) 40% of mucinous and 50% of serous ovarian carcinomas
   c) 40% of Brenner and 50% of germ cell tumors
   d) 40% of mature cystic teratomas and 50% of immature teratomas
   e) 40% of Krukenberg's tumors and 50% of Sertoli-Leydig cell tumors

3. ……solutions are superior for irrigation of the abdominal cavity during endometrioma surgery. Because it is protective against adhesions.
   a) Normal saline (0.9%)
   b) Hypertonic saline (3%)
   c) Lactate Ringer's
   d) 5% dextrose
   e) Mannitol

4. Which one of these is not a conservative treatment option for endometrioma surgery?
   a) Transvaginal Ultrasonography-Guided Aspiration (TUGA)
   b) Laparoscopic Aspiration
   c) Fenestration and Ablation (Fulguration or Vaporization)
   d) Cystectomy
   e) Salpingo-Oophorectomy

5. After……., recurrence of the endometrioma reaches up to 80 to 100%.
   a) Drainage and aspiration
   b) Fenestration
   c) Ablation
   d) Cystectomy
   e) Oophorectomy

6. What is the cutoff value of CA 125 for discriminating ovarian epithelial cancers from endometriomas?
   a) 5 pM
   b) 35 pM
   c) 40 pM
   d) 70 pM
   e) 170 pM

JTGGA CME/CPD CREDITING

Answer form for the article titled *"Ovarian cystectomy in endometriomas: Combined approach"* within the scope of CME/CPD

1st Question	A	B	C	D	E

2nd Question	A	B	C	D	E

3rd Question	A	B	C	D	E

4th Question	A	B	C	D	E

5th Question	A	B	C	D	E

6th Question	A	B	C	D	E

People who answer these questions will receive "2 TMA-CME/CPD credits"

TMA-CME CREDITING BOARD ENQUIRY FORM

JTGGA MANUSCRIPT 2014/15

DATE

TR Identification Number ☐☐☐☐☐☐☐☐☐☐☐ *This form will not be reviewed if TR Identification Number is not stated.*

Name ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Surname ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Signature ..... **The City You Work In** .....

Your Institution .....

IMPORTANT NOTE: You may apply for Turkish Medical Association CME/CPD credits by answering the questions in the front page, filling in your personal information and sending this form to "Abdi İpekçi Cad. No: 2/7 34367 Nişantaşı, İstanbul" by post. This form should arrive to the above-mentioned address latest by November 31, 2014.

JTGGA CME/CPD CREDITING

Questions on the article titled *"Ovarian aging and premature ovarian failure"* within the scope of CME/CPD

1. Which of the following decreases first as a result of the declining cohort of antral follicles?
   a) Estradiol
   b) İnhibin B
   c) İnhibin A
   d) FSH
   e) LH

2. Which one of the following genes affect the rate of initial selection from the primordial follicle pool?
   a) FSHR
   b) LHR
   c) GDF 9
   d) CYP 17
   e) CYP 19

3. Which one of the following is a precursor of sphingolipid secondary messenger and responsible for the cellular silence and physical aging of oocytes?
   a) Ceramide
   b) Advanced glycation end-products
   c) Cu/Zn superoxide dismutase
   d) Gluthation
   e) Telomerase

4. Which one of the following is incorrect for AMH?
   a) AMH is a member of the transforming growth factor-B family
   b) AMH is expressed as early as 36th gestational week
   c) AMH is a dimeric glycoprotein
   d) AMH is secreted from the granulosa cells of pre-antral and small antral follicles
   e) AMH stimulates the early stages of follicular development

5. Which one of the following is the most common etiological factor for premature ovarian failure?
   a) 17α-hydroxylase deficiency
   b) Turner syndrome
   c) Fragile X syndrome
   d) Chemotherapy/Radiotherapy
   e) Type 1 autoimmune polyglandular syndrome

6. Which one of the following chemotherapeutics has high risk for gonadotoxicity?
   a) Cisplatin
   b) Bleomycin
   c) Adriamycin
   d) Vincristine
   e) Cyclophosphamide

JTGGA CME/CPD CREDITING

Answer form for the article titled *"Ovarian aging and premature ovarian failure"* within the scope of CME/CPD

1st Question				
A	B	C	D	E

2nd Question				
A	B	C	D	E

3rd Question				
A	B	C	D	E

4th Question				
A	B	C	D	E

5th Question				
A	B	C	D	E

6th Question				
A	B	C	D	E

People who answer these questions will receive "2 TMA-CME/CPD credits"

TMA-CME CREDITING BOARD ENQUIRY FORM

JTGGA MANUSCRIPT 2014/15

DATE

TR Identification Number ☐☐☐☐☐☐☐☐☐☐☐ *This form will not be reviewed if TR Identification Number is not stated.*

Name ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Surname ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Signature ..... **The City You Work In** .....

Your Institution .....

IMPORTANT NOTE: You may apply for Turkish Medical Association CME/CPD credits by answering the questions in the front page, filling in your personal information and sending this form to "Abdi İpekçi Cad. No: 2/7 34367 Nişantaşı, İstanbul" by post. This form should arrive to the above-mentioned address latest by November 31, 2014.

Türkçe Özler – Eylül 2014

Özgün Araştırma

J Turk Ger Gynecol Assoc 2015; 16: 130-134 • DOI: 10.5152/jtgga.2014.13034

İkinci trimesterde erken doğum indüksiyonu için Misoprostol: Doğum zamanının tahmininde tıbbi öykü ve klinik parametrelerin rolü

Alexander Di Liberto[1], Jan Endrikat[2], Sandra Frohn[2], Erich Solomayer[2], Kubilay Ertan[3]
[1]Department of Obstetrics and Gynecology, Leverkusen Municipal Hospital, Leverkusen, Germany
[2]Department of Obstetrics and Gynecology, Saarland University Hospital, Homburg, Germany
[3]Department of Obstetrics and Gynecology, Leverkusen Municipal Hospital, Leverkusen, Germany

ÖZ

Amaç: Erken gebelikte modern tanı araçları tarafından tespit edilen ciddi fetal malformasyonlar ve/veya kromozom sapmaları hamile kadınlarda indüklenen düşük üzerine tartışmaları gerektirir. Yetkili danışmanlık, tüm düşük işlemi için gerekli zamanın tahmini içerir. Tahminlerimizi rafine etmek için yaptığımız girişimde, 11 tıbbi öykü ve klinik değişkenlerin doğum zamanı üzerine etkisini değerlendirdik.

Materyal ve Metot: Fetal anomali nedeniyle miyadından önce düşük için başvuran 79 kadın hakkında retrospektif kayıt analizi yaptık. Düşük, vajinal misoprostol (prostaglandin E1, CytotecTM, Pfizer, New York, USA) uygulaması ile indüklendi. 11 tıbbi geçmiş ve klinik değişkenlerin 24 saat içinde doğuran kadınların yüzdesi (birincil sonlanım noktası) ve ortalama indüksiyon-doğum zamanı aralığı (ikincil sonlanım noktası) üzerindeki etkilerini araştırdık.

Bulgular: Kadınların %53'ü (42/79) 24 saat içinde doğurdu; %83.6'sı (66/79) 48 saat içinde doğurdu. Geç düşük öyküsü olan kadınların %83.3'ü, öyküsü olmayanların ise %50.7'si 24 saat içinde doğurdu. Ortalama indüksiyon-doğum zamanı aralığı sırasıyla 35.5 saate karşılık 12.3 saat oldu. Erken düşük öyküsü için, rakamlar 24 saat içinde doğum için %48.2'ye karşılık %65.2 ve ortalama indüksiyon-doğum zamanı aralığı için 32.5 saate karşılık 15.6 saat idi. Fetusun güncel ağırlığı >500 g, son önceki yenidoğan ağırlığı ≤3500 g, önceki gebelikler, erken membran rüptürü ve >0.5 mg/dL'lik yüksek CRP de doğum zamanını azalttı. Şaşırtıcı olarak anne ve gebelik yaşı ortalama indüksiyon-doğum zamanı aralığı üzerinde kayda değer veya tutarlı bir etkiye sahip değildi. Farklılıkların hiçbiri istatistiksel olarak anlamlılığa ulaşmadı. Kadınların %83'ü başarılı doğum için 1000 μg veya daha azına ihtiyaç duydu.

Sonuç: Ne tıbbi öykü değişkenleri ne de özel klinik değişkenler ikinci trimesterde doğum zamanının kesin tahminine olanak vermektedir. Bununla birlikte bazı parametreler, indüksiyon-doğum zamanı aralığını azaltmaya bir eğilim göstermektedir. Sonuçlarımız hastaya danışmanlık için bir başlangıç rehberlik olarak hizmet görebilir.

Anahtar kelimeler: Misoprostol, doğum indüksiyonu, doğum zamanı, hastaya danışmanlık

---

Özgün Araştırma

J Turk Ger Gynecol Assoc 2015; 16: 135-139 • DOI: 10.5152/jtgga.2014.13118

Epileptik gebelerde, gebelik sırasındaki nöbet öyküsünün umblikal arter kan gazı sonuçları üzerine etkisi

Özhan Özdemir, Mustafa Erkan Sarı, Funda Arpacı Ertuğrul, Aslıhan Kurt, Vefa Selimova, Cemal Reşat Atalay
Ankara Numune Eğitim ve Araştırma Hastanesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Ankara, Türkiye

ÖZ

Amaç: Çalışmamızda, epileptik gebelerde, gebelik sırasında geçirilmiş olan nöbet sayısının doğum eylemi sırasındaki umblikal arter kan gazı parametreleri üzerine etkisisi olup olmadığının araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Generalize tonik klonik epilepsi tanısı olan, 37-41 gebelik haftaları arasındaki 55 gebe ile benzer özellikleri olan ancak epilepsi tanısı olmayan 50 gebe hasta çalışmaya dahil edildi. Epilepsi tanısı olan hastalar gebelik sırasında en az 5 epileptik nöbet öyküsü olan 27 hasta ve gebelik sırasında nöbeti olmayan 28 hasta olmak üzere iki gruba ayrıldı. Epilepsi tanısı olan gebelerin tamamı geçirilmiş sezaryen öyküsü veya nörolojinin önerisi ile genel anestezi altında sezaryen ile doğum yapmış hastalardı. Bu olgularda doğumdan hemen sonra umbilikal arter kan gazı örneklemesi yapıldı.

Bulgular: Epilepsisi olmayan kontrol grubu ile gebelik sırasında epileptik nöbet öyküsü olmayan gebe kadınlar karşılaştırıldığında umblikal arter kan gazı değerleri açısından fark saptanmadı (p>0.05). Gebelik sırasında 5 ve daha fazla sayıda epileptik nöbet öyküsü olan gebeler, epilepsisi olmayan kontrol grubu ve gebelik sırasında nöbet öyküsü olmayan epilepsili gebelerle karşılaştırıldığında umblikal arter kan pH değeri daha düşük,

parsiyel karbondioksid basıncı (pCO2)daha yüksek ve parsiyel oksijen basıncı (pO2) daha düşük olarak tespit edilse de istatistiki olarak anlamlı fark bulunmamıştır (p>0.05).
Sonuç: Maternal generalize tonik klonik epileptik nöbetler fetus için kaygı verici olabilmektedir. Gebelik sırasındaki tonik klonik nöbetler geçici hipoksi ile ilişkili görünmektedir. Bu nedenle epileptik gebelerde prekonsepsiyonel ve prenatal dönemde, nöbetlere karşı koruyucu olan monoterapi ve en düşük doz ile tedavi amaçlanmalıdır.
Anahtar kelimeler: Epilepsi, gebelik, umblikal arter kan gazı

Özgün Araştırma

J Turk Ger Gynecol Assoc 2015; 16: 140-143 • DOI: 10.5152/jtgga.2014.13102

Vajinal doğum sonrası postpartum idrar retansiyonu: Bir vaka-kontrol çalışmasında risk faktörlerinin değerlendirilmesi

Sabri Cavkaytar, Mahmut Kuntay Kokanalı, Ayşegül Baylas, Hasan Onur Topçu, Bergen Laleli, Yasemin Taşçı
Dr. Zekai Tahir Burak Kadın Sağlığı Eğitim ve Araştırma Hastanesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Ankara, Turkey

ÖZ

Amaç: Vajinal doğum sonrası postpartum idrar retansiyonu için obstetrik risk faktörlerini değerlendirmek.
Materyal ve Metot: Vajinal doğum yapan 234 kadından postpartum idrar retansiyonu olan 19 (%8.1) kadın vaka, retansiyonu olmayan 215 (% 91.9) kadın kontrol idi. Postpartum idrar retansiyonu; işeme sonrası rezidüel ≥150 mL mesane hacmi varlığı veya vajinal doğumdan sonra 6 saat içinde idrar yapamama olarak tanımlandı. Lojistik regresyon analizi idrar retansiyonu için risk faktörlerini belirledi.
Bulgular: Doğum eyleminin ikinci aşamasının süresinin uzaması (OR=0.46,%95 CI için OR=0.06-3.67, p<0.001), epizyotomi varlığı (OR=0.07, 95% CI için OR=0.01-0.68, p=0.022) ve perine yırtılması (OR=97.09,%95 CI için OR=7.93-1188.93, p<0.001), ve yenidoğan için doğum ağırlığının >4000 g olması (OR=0.04,%95 CI için OR=0.01-0.20, p<0.001), vajinal doğum sonrası postpartum idrar retansiyonu için bağımsız risk faktörleri olarak bulundu.
Sonuç: Vajinal doğum sonrası postpartum idrar retansiyonu nispeten sık görülen bir durumdur. Doğum eyleminin ikinci aşamasının uzaması, epizyotomi, perine yırtıkları ve makrozomik doğum dahil olmak üzere risk faktörleri hakkında farkındalık bize bu komplikasyona karşı gerekli önlemlerin alınması için olanak sağlayabilir.
Anahtar kelimeler: Mesane, doğum, risk faktörleri, idrar retansiyonu

---

Özgün Araştırma

J Turk Ger Gynecol Assoc 2015; 16: 144-148 • DOI: 10.5152/jtgga.2014.13047

İntrasitoplazmik sperm enjeksiyonunu uygulanan polikistik over sendromlu kadınlarda obezite kötü gebelik sonuçları ile ilişkili değil

Funda Akpınar, Berfu Demir, Serdar Dilbaz, İskender Kaplanoğlu, Berna Dilbaz
Etlik Zübeyde Hanım Doğum ve Kadın Sağlığı Eğitim ve Araştırma Hastanesi, Tüp Bebek Anabilim Dalı, Ankara, Türkiye

ÖZ

Amaç: Polikistik over sendromlu hastaların vücut kitle indeksinin in vitro fertilizasyon sonuçlarına etkisini değerlendirmek.
Gereç ve Yöntemler: Polikistik over sendromlu hastalara ait 337 siklus vücut kitle indeksine göre normal, kilolu ve obez olarak gruplandırıldı. Stimulasyona cevap, fertilizasyon oranı, implantasyon oranı, klinik ve devam eden gebelik oranları incelendi.
Bulgular: Artan vücut kitle indeksi ile kullanılan total gonadotropin miktarı artarken, oosit sayısının azaldığı görüldü. Siklus iptal oranı, fertilizasyon oranı, implantasyon oranı ve klinik gebelik oranı her üç grupta benzerdi. Kilolu ve obez gruplarda agonist protokol ile antagonist protokole kıyasla daha az siklus iptali oranı ve daha yüksek sayıda oosit eldesi gözlendi.
Sonuç: Obez polikistik over sendromlu kadınların gebelik oranları obeziteden etkilenmedi. Kullanılan protokolünün kilolu ve obez gruplardaki etkisini izlemek üzere daha fazla çalışmaya ihtiyaç vardır.
Anahtar kelimeler: Invitro fertilizasyon, polikistik over sendromu, vücut kitle indeksi

Özgün Araştırma

J Turk Ger Gynecol Assoc 2015; 16: 149-155 • DOI: 10.5152/jtgga.2014.13048

Yaşanılan yer ve yaşam sitilinin gebelikte D vitamini eksikliğine etkisi: Türkiye'nin batı ve doğu uç noktalarının karşılaştırılması

Esra Bahar Gür[1], Gülüzar Arzu Turan[1], Sümeyra Tatar[1], Ayşe Gökduman[2], Muammer Karadeniz[3], Gülnaz Çelik[4], Mine Genç[1], Serkan Çelik[1]
[1]Şifa Üniversitesi Tıp Fakültesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, İzmir, Türkiye
[2]Şifa Üniversitesi Tıp Fakültesi, Biyokimya Anabilim Dalı, İzmir, Türkiye
[3]Department of Endocrinology, Şifa Üniversitesi Tıp Fakültesi, Endokrinoloji Anabilim Dalı İzmir, Türkiye
[4]Şifa Hastanesi, Biyokimya Anabilim Dalı, Erzurum, Türkiye

ÖZ

Amaç: Çalışmamızın amacı, Türkiye'nin en doğu ve en batı noktalarında gebelikte vitamin D eksikliği prevalansını, buna etki eden faktörleri ve "Ulusal gebelikte vitamin D takviyesi programı"na uyumu araştırmaktır.

Gereç ve Yöntemler: Gebeliğin 24-28. haftasındaki gebelere yaşam stilini değerlendiren bir anket uygulandı ve serum 25 hidroksi vitamin D3(25(OH)D3) düzeyleri ölçüldü.

Bulgular: Gebelikte vitamin D eksikilği (≤20 ng/mL) prevalansı İzmir'de %27.8 ve Erzurum'da %76.3 olarak bulundu. "Ulusal gebelikte vitamin D takviyesi programı"na uyum, İzmir'de %8 ve Erzurum'da % 32.6 olarak saptandı. Giyim stili, balık tüketimi, deniz kıyısı tatil süresi ve günlük 1200 IU vitamin D takviyesi, İzmir'de yaşayan gebelerde serum 25(OH)D3 düzeyini etkilerken, sadece tatil süresi ve günlük 1200 IU vitamin D takviyesinin Erzurum'daki gebelerde serum 25(OH)D3 düzeyini etkilediği görüldü. Buna keza, vitamin D eksikliği için kesim noktası olarak ≥32 ng/mL kabul edildiğinde, yaşam stilinin gebelikte serum 25(OH)D3 düzeyine etkisi olmadığı bulundu.

Sonuç: Yaşam sitilinin gebelikte D vitamini düzeyine etkisi özellikle soğuk bölgelerde sınırlıdır. Gebe takibinde, bölge ve mevsim farkı gözetilmeksizin "Ulusal gebelikte vitamin D takviyesi programı"na uyumun arttırılması önerilebilir.

Anahtar kelimeler: Gebelik, D vitamini eksikliği, D vitamini takviyesi, yaşam stili, yaşanılan yer

---

Özgün Araştırma

J Turk Ger Gynecol Assoc 2015; 16: 156-160 • DOI: 10.5152/jtgga.2014.13068

Bir ardışık kültür besiyeri ortamında morfokinetik verilere dayalı hızlandırılmış embriyo seçimi modelinin tekrarlanabilirliği

Ender Yalçınkaya, Elif G. Ergin, Eray Çalışkan, Zeynep Öztel, Alev Özay, Hakan Özörnek
Eurofertil Tüp Bebek Merkezi, İstanbul, Türkiye

ÖZ

Amaç: Önceden yapılanmış embriyo skorlama modeline dayalı dinamik skor verilen embriyoların akıbetini karşılaştırmak ve bu modelin bizim verilerimiz ile uyumlu olup olmadığını analiz etmek.

Materyal ve Metot: Bu çalışmada bilinen implantasyon verileri ile transfer edilen toplam 910 embriyo retrospektif olarak analiz edildi. Tüm embriyolara önceden yapılanmış hiyerarşik embriyo skorlama modeline dayalı bir dinamik skor verildi.

Bulgular: En yüksek gebelik oranı C + ve A- (her biri için %48.2) gruplarında görüldü ve en düşük E grubunda (%19.7) gözlendi. İmplantasyon ve klinik gebelik oranları gruplar arasında karşılaştırıldığında, en yüksek ve istatistiksel olarak anlamlı implantasyon ve klinik gebelik oranları grup C +'te görüldü (her biri için %32.7, p=0.000). Bu oranlar grup A-'da %29.4'e geriledi.

Sonuç: Dinamik skora göre embriyoların akıbetleri önceden yapılanmış modelin sonuçları ile uyumlu değildir. Her IVF laboratuvarı kendi uygulamalarına dayanarak benzersizdir. Bu nedenle, her IVF laboratuvarının önceden yapılanmış bir modeli kullanmak yerine kendi verilerine dayanan kendi embriyo seçim kriterlerini belirlemesi gerektiğini düşünmekteyiz.

Anahtar kelimeler: Önceden yapılanmış model, dinamik skor, gebelik oranı

Özgün Araştırma

J Turk Ger Gynecol Assoc 2015; 16: 161-163 • DOI: 10.5152/jtgga.2014.13091

Oositlerde gözlenen perivitelline aralık bozukluklarının embryo gelişimi üzerine etkisi

Hikmet Hassa, Yunus Aydın, Fulya Taplamacıoğlu
Eskişehir Osmangazi Üniversitesi Tıp Fakültesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Eskişehir, Türkiye

ÖZ

Amaç: Yardımcı üreme teknikleri ile elde edilen embriyoların kalitesini etkileyen en önemli faktörlerden bir tanesi oosit kalitesidir. Oosit kalitesi ise sitoplazmik ve ekstrasitoplasmik olgunlaşmaya bağlıdır. Bu çalışmanın amacı; ekstrasitoplazmik olgunlaşmada ki önemli faktörlerden olan perivitelline aralık özelliklerinin embryo gelişimi üzerine etkisini incelemektir.

Gereç ve Yöntemler: Bu çalışmada erkek faktör infertilitesi nedeniyle gonadotropin-releasing hormone (GnRH) analog + recombinant Follicle-stimulating hormone (rec-FSH) (mid-luteal uzun protokol) ile stimulasyon uygulanan 98 intracytoplasmic sperm injection (ICSI) siklusundan elde edilen 1154 oositten, kriterlere uygun olan 217 oosit değerlendirilmiştir. Perivitelline aralık anormalliği (genişleme ± granüler yapı) olan 105 metafaz-II oosit ile tamamen normal olan 112 metafaz-II oosit, embryo geliştirebilme özelliklerine göre karşılaştırılmışlardır. Normal metafaz-II oosit; yuvarlak ve parlak zona pelusida, sitoplazmik membrane etrafında boşluk içermeyen ancak parçalanmamış birinci polar cisimciği içeren perivitelline aralık, homojen ve orta derecede granuler yapı gösteren sitoplazma ile karakterizedir. Oosit ve embryo değerlendirmeleri Alpha Scientists in Reproductive Medicine and the European Society of Human Reproduction and Embryology (ESHRE) Special Interest Group of Embryology kriterlerine göre yapılmıştır.

Bulgular: 105 perivitelline anormalliği olan oositten Grade-I, II ve III embryo gelişme oranı sırası ile 68.5%, 23.8% ve 7.7% idi. 112 normal oositten Grade-I, II ve III embryo gelişme oranı sırası ile 82.1%, 17.9% ve 0% idi. Grade-I (68.5% vs. 82.1%, p value; 0.019) ve Grade-III (7.7% vs. 0%, p value; 0.003) embryo geliştirebilme oranları perivitelline aralık anormalliği olan oositler ile daha düşüktü.

Sonuç: Oosit kalitesi değerlendirilirken perivitelline aralık özellikleri de değerlendirilmelidir. Özellikle erkek faktörü nedeniyle GnRH analog + rec FSH ile stimulasyon uygulanan hastalarda elde edilen oositlerde, perivitelline aralık anormallikleri embryo gelişimini kötü yönde etkileyebilir.

Anahtar kelimeler: Embryo, oosit, perivitelline aralık

Özgün Araştırma

J Turk Ger Gynecol Assoc 2015; 16: 164-172 • DOI: 10.5152/jtgga.2014.13109

Endometriyum kanseri olan hastalarda omental metastazın önemi nedir?

Taner Turan[1], Işın Üreyen[1], Alper Karalök[1], Tolga Taşçı[1], Hilal Ilgın[1], Levent Keskin[2], M. Faruk Kose[1], Gökhan Tulunay[1]
[1]Etlik Zübeyde Hanım Kadın Sağlığı Eğitim ve Araştırma Hastanesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Ankara, Türkiye
[2]Ankara Atatürk Eğitim ve Araştırma Hastanesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Ankara, Türkiye

ÖZ

Amaç: Omental metastazı olan endometriyum kanserli hastalarda cerrahi-patolojik faktörleri, sağkalımı ve sağkalımı belirleyen faktörleri belirlemek.

Gereç ve Yöntemler: Hastanemizde 1993-2012 yılları arasında opere edilen ve omental metastazı olan hastalar dahil edildi. Eşlik eden başka tümörü olan ve uterin sarkomu olan hastalar çalışmaya dahil edilmedi.

Bulgular: Omentektomi endometriyum kanseri olan 811 hastaya uygulandı ve omental metastaz hastaların 48'inde (5.9%) tespit edildi. Tümör tipi 26 hastada endometrioid tipti. Omental metastaz hastaların %60 ve %40'ında sırasıyla makroskopik ve mikroskopikti. Total omentektomi mikroskopik metastazların yakalanma ihtimalini arttırıyordu. Omental metastazı olan hastaların %68.8'inde pozitif peritoneal sitoloji, %66.7'sinde adneksiyal tutulum, %60.5'inde lenfatik tutulum, %47.9'unda servikal metastaz ve %29.2'sinde serozal tutulum vardı. Bu hastaların %43.8'inde omentum, adneks ve peritoneal sitoloji dışı intraabdominal tutulum vardı. İki yıllık hastalıksız sağkalım %28.2 iken 2 yılık toplam sağkalım %40 idi. Myometrial invazyon derinliği, grade, sitoloji ve pelvik lenf nodlarının durumu 2 yıllık hastalıksız sağkalımla ilişkili iken servikal invazyon ve sitoloji 2 yıllık toplam sağkalımla ilişkili idi.

Sonuç: Endometriyum kanserinde omental metastaz kötü prognoz demektir ve 2. yılın sonunda hastaların üçte ikisi kaybedilir. Total omentektomi mikrometastazların yakalanma şansını arttırsa da sağkalıma etkisi tartışmalıdır. Bu hasta grubunda yeni tedavi modaliteleri gerekmektedir.

Anahtar kelimeler: Endometriyum kanseri, omental metastaz, sağkalım

Özgün Araştırma

J Turk Ger Gynecol Assoc 2015; 16: 173-176 • DOI: 10.5152/jtgga.2014.13130

İzole intrauterin gelişme geriliği ve preeklampsi ile birlikte intrauterin gelişme geriliği olan kadınlarda serum maternal adiponektin konsantrasyonlarının karşılaştırılması

Barış Büke[1], Hasan Onur Topçu[1], Yaprak Engin-Üstün[2], Nuri Danışman[2]
[1]Ege Üniversitesi Tıp Fakültesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, İzmir, Türkiye
[2]Zekai Tahir Burak Kadın Sağlığı Eğitim ve Araştırma Hastanesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Ankara, Türkiye

ÖZ

Amaç: Bu çalışmanın amacı izole intrauterin gelişme geriliği (IUGG) olan gebe kadınlarda ve preeklampsi ile birlikte IUGG olan (IUGG+PE) gebe kadınlarda serum maternal adiponektin konsantrasyonlarını karşılaştırmaktı.

Materyal ve Metot: Yaşları 18-40 arası, izole IUGG olan otuz hasta (grup 1), IUGG+PE olan 20 hasta (grup 2) ve 30 sağlıklı kontrol (grup 3) çalışmaya dahil edildi. Bu hastaların venöz kan örnekleri aç durumda elde edildi. Adiponektin konsantrasyonları santrifüj sonrası elde edilen serumda enzim-bağlı immünosorbent deneyi ile ölçüldü. Gruplar arasındaki farklılıkları bulmak için, student t-testi ve tek yönlü ANOVA istatistiksel metotları kullanıldı.

Bulgular: Gruplar arasında yaş, vücut kitle indeksi, gebelik yaşı ve parite açısından fark yoktu ($p>0.05$). Üç grup arasında karşılaştırıldığında amniotik sıvı indeksi değerleri ($p<0.001$) ve gebelik sırasında kazanılan ağırlık ($p=0.017$) anlamlı olarak farklıydı. Adiponektin ortalama konsantrasyonları IUGG grubunda 94.041 pg/mL, IUGG+PE grubunda 55.717 pg/mL ve kontrol grubunda 51.831 pg/mL idi. Hem IUGG ve IUGG+PE grupları (p değeri; <0.05) hem de IUGG ve kontrol grupları arasındaki farklar istatistiksel olarak anlamlı idi (p değeri; <0.001). Bununla birlikte, IUGG+PE grubu ve kontrol grubu arasında anlamlı bir fark yoktu ($p>0.05$).

Sonuç: IUGG'nin maternal serum adiponektin konsantrasyonlarını artırdığını bulduk, bununla birlikte bu artış IUGG+PE olan gebe kadınlarda oluşmaz.

Anahtar kelimeler: IUGG, preeklampsi, adiponektin

Derleme

J Turk Ger Gynecol Assoc 2015; 16: 177-189 • DOI: 10.5152/jtgga.2014.1111

Endometriomalarda over kistektomisi: Kombine yaklaşım

Cihat Ünlü[1], Gazi Yıldırım[2]
[1]Acıbadem Üniversitesi, Bakırköy Acıbadem Hastanesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, İstanbul, Türkiye
[2]Yeditepe Üniversitesi Hastanesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, İstanbul, Türkiye

ÖZ

Endometrioma premenopozal popülasyonda en sık adneksiyal kitlelerden biridir, ancak önerilen tedavi hâlâ tartışma konusudur. Tıbbi tedavi etkisizdir ve over endometriomalarının tedavisinde önerilemez. Genel görüş birliği hem ağrıyı azaltmak hem de spontan gebelik oranlarını artırmak için 4 cm'den büyük over endometriomalarının çıkarılması gerektiğidir. Kapsül genellikle yoğun yapışık olduğu için over endometriomalarının çıkarılması zor olabilir. Seçilecek cerrahi tedavi cerrahi laparoskopi iken, konservatif tedavi için tercih edilen metot modifiye kombine kistektomidir. Kistektomi over için zarar verici olabilir oysa daha fazla rekürrens riski ile birlikte ablasyon yetersiz olabilir. Bizim bilgimize göre, modifiye kombine teknik endometrioma tedavisinde daha etkili olarak görülmektedir.

Anahtar kelimeler: Endometrioma, laparoskopi, kistektomi, kombine teknik

Derleme

J Turk Ger Gynecol Assoc 2015; 16: 190-196 • DOI: 10.5152/jtgga.2014.0022

Ovaryen yaşlanma ve prematür over yetmezliği

Yavuz Emre Şükür[1], İçten Balık Kıvançlı[2], Batuhan Özmen[1]
[1]Ankara Üniversitesi Tıp Fakültesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Ankara, Türkiye
[2]Gazimagusa Devlet Hastanesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Gazimagusa, Kuzey Kıbrıs Türkiye Cumhuriyeti

ÖZ

Üremede fizyolojik yaşlanma ovaryen korteks folliküllerindeki oositlerin sayı ve kalitesinde azalma sonucunda ortaya çıkar. Her ne kadar havuz ve folliküler oosit kalitsindeki azalmanın nedeni tam olarak anlaşılamamışsa da, endokrin, parakrin, genetik ve metabolik faktörlerin etkili olduğu düşünülmektedir. Günümüzde, ovaryen yaşlanma mekanizmalarını anlayabilmek açısından genomik araştırmalar önem kazanmıştır. Ovaryen yaşlanma sürecindeki, telomeraz ve seramid gibi ko-faktörlerin etkileri yeni araştırmalarla incelenmektedir. Ovaryen yaşlanmanın değerlendirilmesinde en önemli testler antral follikül sayısı ve antimülleryan hormondur.
Anahtar kelimeler: Ovaryen yaşlanma, prematür over yetmezliği, üreme

---

Olgu Sunumu

J Turk Ger Gynecol Assoc 2015; 16: 197-200 • DOI: 10.5152/jtgga.2014.76736

Uterusun multiloküle kistik Mullerianosisi: Bir olgu sunumu

Pattomthadathil Sankaran Jayalakshmy, Shasi Velusamy, Joy Augustine
Department of Pathology, Government Medical College Thrissur, Kerala, India

ÖZ

Uterus fundusunun serozal yüzeyinde multiloküle kistik kitle olarak ortaya çıkan bir Mullerianosis olgusu rapor etmekteyiz. Klinik ve radyolojik olarak, bir over tümörü olarak yorumlandı. Mullerianosis çok nadir benign tümör benzeri lezyondur. Bu lezyon hakkında farkındalık; klinisyenler, radyologlar ve patologların yanlış tanıdan kaçınmaları için gereklidir.
Anahtar kelimeler: Uterus fundusu, Mullerianosis, multiloküle kistik kitle

---

Olgu Sunumu

J Turk Ger Gynecol Assoc 2015; 16: 201-203 • DOI: 10.5152/jtgga.2014.37268

Persistan asit nedeniyle over kanserini taklit eden sklerozan kapsüle edici peritonit: Olgu sunumu

Mete Çağlar[1], Nilüfer Çetinkaya[2], Emre Özgü[2], Tayfun Güngör[2]
[1]Düzce Üniversitesi Tıp Fakültesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Düzce, Türkiye
[2]Zekai Tahir Burak Kadın Sağlığı Eğitim ve Araştırma Hastanesi, Jinekolojik Onkoloji Anabilim Dalı, Ankara, Türkiye

ÖZ

'Koza Sendromu' olarak da bilinen sklerozan kapsüle edici peritonit intra-abdominal organları saran, kalın, fibrotik bir kese varlığı nedeniyle barsak tıkanıklığı, karın ağrısı ve persistan asite yol açan nadir bir durumdur. Sendrom konjenital olabileceği gibi çeşitli faktörler nedeniyle edinsel olarak da görülebilmektedir ve nonspesifik semptomlarla seyretmektedir. Sendroma ait primer patogenez net olarak tanımlanamasa da genetik

faktörler, etken ajanların transtubal yolla karın boşluğuna ulaşması, peritoneal enfeksiyonlar, farmakolojik ajanlar ve invazif peritoneal girişimler etkili olabilmektedir. Sendroma ait spesifik tanı kriterleri olmayıp çoğu olgu operasyon sırasında barsak segmentlerini saran kalın, fibrotik kesenin gözlenmesiyle tanı almaktadır. Fibrotik kese peritoneal sıvı dinamiğini değiştirmekte ve persistan asite yol açmaktadır. Yazımızda preoperatif dönemde büyük heterojen kitlesi ve asit varlığı nedeniyle over kanseri ön tanısıyla opere edilen ancak peroperatif olarak Abdominal Koza Sendromu tanısı alan bir olguyu sunarak bu konuya dikkat çekmeyi planladık.

Anahtar kelimeler: Abdominal koza sendromu, sklerozan kapsüle edici peritonit, asit