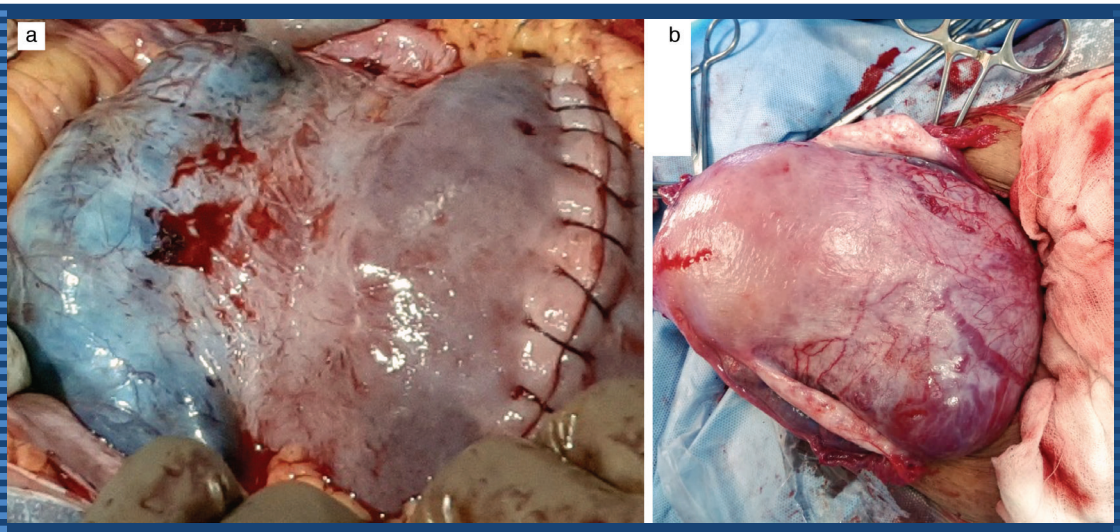
ISSN 1309-0399 • EISSN 1309-0380

TURKISH-GERMAN GYNECOLOGICAL EDUCATION and RESEARCH FOUNDATION

Journal of the Turkish-German Gynecological Association



Volume 21
Issue 4
December
2020

Cover Picture: Khoiwal et al. A multi-modal management of placenta percreta

galenos yayınevi

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

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

Owned by on behalf of the Turkish German Gynecology Education, Research Foundation / Türk Alman Jinekoloji Eğitim Araştırma ve Hizmet Vakfı adına sahibi: M. Cihat Ünlü
Published by Turkish German Gynecology Education, Research Foundation / Türk Alman Jinekoloji Eğitim Araştırma ve Hizmet Vakfı tarafından yayınlanmaktadır.
Abdi İpekçi Cad. 2/7 34367 Nişantaşı, İstanbul, Turkey

galenos yayınevi

Galenos Publishing House
Owner and Publisher
Derya Mor
Erkan Mor

Publication Coordinator
Burak Sever

Web Coordinators
Fuat Hocalar
Turgay Akpınar

Graphics Department
Ayda Alaca
Çiğdem Birinci
Gülşah Özgül

Finance Coordinator
Sevinç Çakmak

Project Coordinators
Duygu Yıldırım
Gamze Aksoy
Gülay Akın
Hatice Sever
Melike Eren
Özlem Çekil
Pınar Akpınar
Rabia Palazoğlu

Research&Development
Mert Can Köse
Mevlüde Özlem Küççük

Digital Marketing Specialist
Seher Altundemir

Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1
34093 İstanbul, Turkey
Phone: +90 (212) 621 99 25 **Fax:** +90 (212) 621 99 27
E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr **Publisher Certificate Number:** 14521

Printing at: Özgün Basım Tanıtım San. Tic. Ltd. Şti.
Yeşilce Mah. Aytekin Sok. Oto Sanayi Sitesi No: 21 Kat: 2
Seyrantepe Sanayi, Kağıthane, İstanbul, Turkey
Phone: +90 (212) 280 00 09 **Certificate Number:** 48150
Printing Date: December 2020
ISSN: 1309-0399 **E-ISSN:** 1309-0380
International scientific journal published quarterly.

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. 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 reviewers and authors.

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

Journal of the Turkish-German Gynecological Association is indexed in PubMed, PubMed Central, Thomson Reuters – Emerging Sources Citation Index, EMBASE, Scopus, CINAHL, EBSCO, ProQuest, DOAJ, Index Copernicus, ARDI, GOALI, Hinari, OARE, J-GATE, TÜBİTAK ULAKBİM TR Index, Türk Medline, EuroPub, IdealOnline and Turkiye Citation Index.

Open Access Policy

This journal provides immediate open access to its content on the principle that making research freely available to the public supporting a greater global exchange of knowledge.
Open Access Policy is based on rules of Budapest Open Access Initiative (BOAI) http://www.budapestopenaccessinitiative.org/. By "open access" to [peer-reviewed research literature], we mean its free availability on the public internet, permitting any users to read, download, copy, distribute, print, search, or link to the full texts of these articles, crawl them for indexing, pass them as data to software, or use them for any other lawful purpose, without financial, legal, or technical barriers other than those inseparable from gaining access to the internet itself. The only constraint on reproduction and distribution, and the only role for copyright in this domain, is right of authors to retain control over the integrity of their work and the right to be properly acknowledged and cited.

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, required for use any published under CC BY-NC-ND license with commercial purposes (selling, etc.) to protect copyright owner and author rights, 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 Galenos.

The journal is printed on acid-free paper.

OPEN ACCESS

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, and commentaries in the fields of Gynecology, Gynecologic Oncology, Endocrinology & Reproductive Medicine and Obstetrics. Case reports are not accepted for publication. Reviews will be considered for publication only if they are prepared by authors who have at least three published manuscripts in international peer reviewed journals and these studies should be cited in the review. Otherwise only invited reviews will be considered for peer review from qualified experts in the area.

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 December 2016, 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 ORCID (Open Researcher and Contributor ID) number of the all authors should be provided while sending the manuscript. A free registration can be done at http://orcid.org.

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 300 DPI.

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. All manuscripts submitted to the journal for publication are checked by Crossref Similarity Check powered by iThenticate software for plagiarism. If plagiarism is detected, relevant institutions may be notified. In this case, the authors might be asked to disclose their raw data to relevant institutions.

Peer-Review Process

Each manuscript submitted to Journal of the Turkish-German Gynecological Association is subject to an initial review by the editorial office in order to determine if it is aligned with the journal's aims and scope, and complies with essential requirements. Manuscripts sent for peer review will be assigned to one of the journal's associate editors that has expertise relevant to the manuscript's content. All accepted manuscripts are sent to a statistical and English language editor before publishing. Once papers have been reviewed, the reviewers' comments are sent to the Editor, who will then make a preliminary decision on the paper. At this stage, based on the feedback from reviewers, manuscripts can be accepted, rejected, or revisions can be recommended. Following initial peer-review, articles judged worthy of further consideration often require revision. Revised manuscripts generally must be received within 3 months of the date of the initial decision. Extensions must be requested from the Associate Editor at least 2 weeks before the 3-month revision deadline expires; Journal of the Turkish-German Gynecological Association will reject manuscripts that are not received within the 3-month revision deadline. Manuscripts with extensive revision recommendations will be sent for further review (usually by the same reviewers) upon their re-submission. When a manuscript is finally accepted for publication, the Technical Editor undertakes a final edit and a marked-up copy will be e-mailed to the corresponding author for review and to make any final adjustments.

Journal of the
Turkish-German
Gynecological Association

Instructions for Authors

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 1964 Declaration of Helsinki, as revised in 2013. 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.

In experimental animal studies, the authors should indicate that the procedures followed were in accordance with animal rights as per the Guide for the Care and Use of Laboratory Animals (http://oacu.od.nih.gov/regs/guide/guide.pdf) and they should obtain animal ethics committee approval.

The editors reserve the right to reject manuscripts that do not comply with the above-mentioned requirements. The author will be held responsible for false statements or for failure to 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 state whether or not there is the absence or presence of a conflict of interest. They 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 evaluation site. The copyright transfer form should be signed by all contributing authors and a scanned version of the wet signed document should be submitted.

COPYRIGHT TRANSFER FORM

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.

Journal of the
Turkish-German
Gynecological Association

Instructions for Authors

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. The abstract should be limited to 250 words for original articles and review articles.

Keywords

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

Original manuscripts 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 and strenghts of the study. No new data are to be presented in this section.

Reviews must contain the section with critical evaluation and inefficiacy of evidences and explanations to guide further studies in the end.

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 preeclampsia, 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.

Review Article: Review articles are comprehensive analyses of specific topics in medicine. All review articles will undergo peer review prior to acceptance. Review articles must not exceed 5000 words for the main text (excluding references, tables, and figure legends) and 400 words for the abstract. A review article can be signed by no more than 5 authors and can have no more than 80 references. Also there should be references to authors' own two works.

Editorial: Editorials are a brief remark on an article published in the journal by the reviewer of the article or by a relevant authority. Most comments are invited by the Editor-in-Chief but spontaneous comments are welcome. It must not exceed 700 words (excluding references). An abstract is not required with this type of manuscripts. It can have no more than 15 references and 1 figure or table.

Letter to the Editor: Letters in reference to a journal article must not exceed 500 words (excluding references). Letters not related to a journal article must also not exceed 500 words (excluding references). An abstract is not required with this type of manuscripts. A letter can be signed by no more than 4 authors and can have no more than 5 references and 1 figure or table.

Tables and Figures

Tables should be included in the main document after the reference list. Color figures or gray-scale images must be at minimum 300 DPI resolution. Figures should be submitted in "*.tiff", "*.jpg" or "*.pdf" format and should not be embedded in the main document. Tables

Instructions for Authors

and figures consecutively in the order they are referred to within the main text. Each table must have a title indicating the purpose or content of the table. Do not use internal horizontal and vertical rules. Place explanatory matter in footnotes, not in the heading. Explain all abbreviations used in each table in footnotes. Each figure must have an accompanying descriptive legend defining abbreviations or symbols found in the figure. If photographs of people are used, the subjects must be unidentifiable and the subjects must have provided written permission to use the photograph. There is no charge for color illustrations.

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. The second plagiarism check will be made after revision.

Accepted Articles

Epub Ahead of Print

The abstract of the accepted manuscripts will be shown in PubMed as "Epub ahead of print".

An "Epub ahead of print" signifies that the electronic version of an article has been published online (at PubMed and the journal's website www.jtgga.org), but that the print version of the article has not yet been published.

If an article was published online ahead of print, the date it was published online, along with the digital object identifier (DOI) to ensure that all article versions can be identified, should follow the acceptance date footnote (or, if the journal does not publish the acceptance date, it should be placed first).

Journal and Society Web sites:

www.dtgg.de
(Deutsch-Türkische Gynäkologengeselleschaft)

www.tajev.org
(Turkish-German Gynecological Education and Research Foundation)

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

Contents

Journal of the
Turkish-German
Gynecological Association

Editorial

Dear Colleagues,

It is my great pleasure to present you the fourth issue of the "Journal of the Turkish-German Gynecological Association (J Turk Ger Gynecol Assoc)" in the publishing year of 2020.

Over 800 women are dying each day from complications in pregnancy and childbirth. Haemorrhage remains the leading cause of maternal deaths. Placenta accreta spectrum is an important cause of maternal hemorrhage and its prevalence is likely to increase. Here you will read a paper aiming to identify an optimum management option to improve maternal outcomes in patients with placenta percreta based on the available literature.

You will also read an interesting paper investigating the effects of hysterosalpingography, with and without iodinated contrast, on endometrium, tubes and ovarian epithelial cells in an animal model.

Also you will get the occasion to read both a review discussing treatment protocols for patients with gynecological cancers during the global coronavirus disease-2019 (COVID-19) pandemic and a paper about how gynecologic oncologists modified their patient management during COVID-19 in Turkey.

Dear authors and reviewers,

"Peer Review Week 2020" was celebrated on September 21-25. It is a yearly international event celebrating the pivotal role that peer review plays in maintaining scientific quality. It was started in 2015 by Sense About Science, Peer Review Evaluation, ORCID, ScienceOpen and Wiley-Blackwell to highlight the importance of peer review in academic societies. Transparency (easily discoverable, accessible, and clear), quality, trust are all important issues in the peer review process. It is time-consuming. At JTGGA, we are piloting several new innovations in peer review to speed up the policy and to make the process more transparent. We provide details about the number of reviewers who reviewed the article in response letter. In addition, the citation rates of our journal continue to increase gradually in the last quarter of the year compared to the previous year. In the upcoming period, we hope that our journal will receive more citations and we will be honored to share the developments with you.

We would like to thank all our peer reviewers. We appreciate your hard work and dedication to ensuring the highest scientific standards.

Best regards,

Prof. Cihat Ünlü, M.D.
Editor in Chief of *J Turk Ger Gynecol Assoc*
President of TGGF

Influence of evening/night-time birth on maternal/perinatal outcomes in a low-risk population

Cláudia Rejane Pinheiro Maciel Vidal[1], Maxsuenia Queiroz Medeiros[1], Joana Adalgisa Furtado Magalhães Andrade[1], Edward Araujo Júnior[2,3], Francisco Herlânio Costa Carvalho[1]

[1]Department of Obstetrics and Gynecology, University of Ceará (UFC), Assis Chateaubriand Maternity School, Fortaleza-CE, Brazil
[2]Department of Obstetrics, Paulista School of Medicine - Federal University of São Paulo (EPM-UNIFESP), São Paulo-SP, Brazil
[3]Medical course, Municipal University of São Caetano do Sul (USCS), São Paulo-SP, Brazil

Abstract

Objective: To compare maternal and perinatal outcomes between day-time and evening/night-time births in a low-risk population.

Material and Methods: The present study had a retrospective and cross-sectional design. The study recruited 421 pregnant women admitted for spontaneous or induced labor, with singleton, full-term pregnancy, without comorbidities, and with birthweight between 2,500 and 4,499 g. Maternal data, including severe bleeding, need for blood transfusion, puerperal infection, and admission to the intensive care unit, and neonatal data including birthweight, Apgar scores at first and fifth minute, oxygen administration, resuscitation, admission to the neonatal care unit, infection, and blood transfusion, were evaluated. Univariate and multivariate analysis and calculation of the prevalence ratio (PR) were performed with a 95% confidence interval (CI).

Results: There were no differences in factors of maternal morbidity between delivery times. Newborns delivered during the evening/night-time had a higher prevalence of infection (15.3% vs 7.9%, p=0.019, PR: 2.11, CI 95% 1.13-3.93) and hospitalization in the neonatal care unit (25.8% vs 10.4%, p<0.001, PR: 2.99, CI 95% 1.76-5.10). There was no difference in other perinatal morbidities examined.

Conclusion: Evening/night-time births were associated with a higher prevalence of infection and the need for admission to an intensive care unit. (J Turk Ger Gynecol Assoc 2020; 21: 221-7)

Keywords: Evening/night-time, labor, delivery, adverse maternal/perinatal outcomes

Received: 22 May, 2020 **Accepted:** 03 September, 2020

Introduction

In Brazil, and worldwide, the emphasis on humanized childbirth care has increased. In this model of humanized childbirth, several measurements are adopted to improve access, reception, quality, and resolution of obstetric care; actions that are important to reduce maternal and perinatal morbidity (1).

The Brazilian Ministry of Health, which aims to provide better maternal and perinatal outcomes, has created public policies that seek to improve the quality of maternal and child healthcare. Despite expanding prenatal care, delivery, and newborn care, maternal and perinatal mortality rates are still high, as evidenced by intense hospitalization and medicalization of childbirth (2,3).

A higher risk of adverse perinatal outcomes among parturients admitted during off-hours (weekends, evening, during the night) compared to office hours, has led to questions about the quality of care provided during off-hours (4,5). According to de Graaf et al. (6), these findings are evidence of organizational problems that directly affect perinatal outcomes. According to Gijsen et al. (7) evening and nighttime deliveries are associated with a higher risk of adverse perinatal outcomes when compared with daytime deliveries. These risks are concentrated in subgroups

Address for Correspondence: *Edward Araujo Júnior*
e.mail: araujojred@terra.com.br ORCID: orcid.org/0000-0002-6145-2532

Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2020.2020.0081

that involve induction or augmentation of labor or emergency cesarean section.

In Brazil, no studies have analyzed the childbirth care received by parturients in maternity hospitals during the day, in the evening, or at night. The study objective was to compare maternal and perinatal outcomes between daytime and nighttime births in a low-risk population in a tertiary healthcare setting.

Material and Methods

The present study was a cross-sectional study with a retrospective design. Data was collected from medical records and birth notification forms from April 1st, 2014 to March 31st, 2015. The research complied with resolution no 466/2012 of the National Health Council and was approved by the local ethics committee (approval number: 957,050).

To compose the sample, a finite size calculation was performed with a 95% confidence interval (CI) and a maximum error of 5%, resulting in a sample size of 351 based on the number of deliveries in the period of one year, between 2014 and 2015 with 4,099 deliveries performed. In addition, 20% was added to cover participant drop-out, thus resulting in a final recruitment target of 421 participants.

The study included parturients admitted to the obstetric center during spontaneous or induced labor with a live fetus upon admission, and with singleton, full-term pregnancy and without comorbidities, which included a history of diabetes and/or chronic or gestational arterial hypertension, human immunodeficiency virus infection, and/or positive venereal diseases research laboratory. Fetal birth weights should be between 2,500 g and 4,499 g. Parturients admitted for elective cesarean section were excluded. For the purpose of the study daytime hours were defined as 7.00 a.m. to 6.59 p.m. and evening/nighttime hours as 7.00 p.m. to 6.59 a.m. This division was due to standardization of staff shift patterns. Mother and baby pairs were divided into two groups based on delivery falling into one of these two time groupings.

Initially, a list of 729 patient names was constructed. The list included patients who had given birth in that period following examination of neonatology records. After further examination of patients' medical records, 172 women were removed because they did not meet the inclusion criteria. A total of 136 medical records were requested but were not available. Therefore, the final sample consisted of 421 women and their newborns, since there were no fetal or neonatal deaths (Figure 1).

Epidemiological and obstetric care data were collected. Data items collected were in four basic categories. These were: i) sociodemographic characteristics including race, age, marital status and education; ii) obstetric clinical characteristics including number of pregnancies (including the current pregnancy), number of previous cesarean sections, number of prenatal consultations, Robson's classification, type of delivery, professional who attended the delivery; iii) maternal morbidity including severe bleeding, need for blood transfusion, puerperal infection, and admission to the intensive unit care (ICU); and iv) neonatal morbidity including Apgar scores at 1st and 5th minute, need for oxygen, resuscitation in the delivery room, admission to the neonatal ICU, neonatal jaundice, history of infection and blood transfusion.

Statistical analysis

The data was analyzed using Stata® 11.2 software (Stata Corp., College Station, TX, USA). Univariate analysis was performed, with the calculation of proportions for categorical variables and measurements of central tendency for numerical variables. The differences between the study groups were assessed for statistical significance using the chi-squared test or Fisher's exact tests for categorical variables. A significance level of $p<0.05$ was considered statistically significant. The prevalence ratio (PR) was calculated with a 95% CI.

Results

Table 1 shows the comparison of sociodemographic and obstetric characteristics among the participants according to the two birth times. Of the 421 deliveries, 190 (45.1%) occurred during the evening/night-time, while 231 (54.9%) occurred during the day-time. There was a predominance of patients who were non-white and a higher proportion of women aged 20-35 years (63.6%). Regarding relationship status, 74.7% of patients had a partner. In educational terms, 56.3% had attended high school, while 54.2% of participants were primiparous. The majority of patients (64.5%) had at least six prenatal consultations and had not previously undergone cesarean section (93.7%) (Table 1).

When the parturients were separated by Robson's classification, there was no statistical difference between the period of delivery. 99.1% of the women involved in the study were classified in the

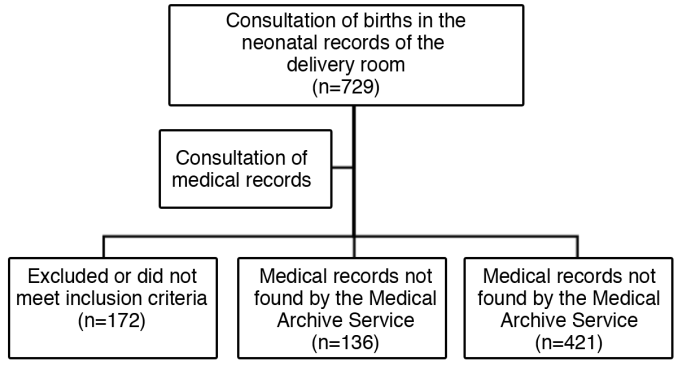


Figure 1. Recruitment of the participants

Table 1. Sociodemographic and obstetric characteristics according to the birth time

Variable	Day	Evening/night	PR (CI 95%)	p
	n (%)	n (%)		
	231 (100.0)	190 (100.0)		
Race				
Non-white	150 (64.9)	129 (67.9)	1.08 (0.49-2.38)	0.849[d]
White	14 (6.1)	13 (6.8)		
No information	67 (29.0)	48 (25.3)		
Age (years)				
<20	77 (33.3)	64 (33.7)	0.91 (0.61-1.36) 1.59 (0.58-4.35)	0.366[d]
20-35	147 (63.6)	117 (61.6)		
>35	7 (3.0)	9 (4.7)		
Marital status				
Without partner	56 (24.2)	48 (25.3)	0.96 (0.62-1.50)	0.869[d]
With partner	172 (75.4)	142 (74.7)		
No information	3 (1.3)	0 (0)		
Scholarity				
Elementary school	93 (40.3)	80 (42.1)	0.88 (0.59-1.30) 1.38 (0.52-3.66)	0.522[d]
High school	130 (56.3)	101 (53.2)		
University	8 (3.5)	9 (4.7)		
Number of pregnancies				
Primiparous	116 (50.2)	103 (54.2)	0.85 (0.57-1.25)	0.414[d]
Multiparous	115 (49.8)	87 (45.8)		
Number of previous cesarean sections				
0	207 (89.6)	178 (93.7)	1.64 (0.80-3.40) 0.67 (0.32-1.40)	0.177[d]
1	21 (9.1)	12 (6.3)		
≥2	2 (0.9)	0 (0.0)		
No information	1 (0.4)	0 (0)		
Number of prenatal care consultations				
<6	82 (35.5)	71 (37.4)	0.92 (0.62-1.37)	0.691[d]
≥6	149 (64.5)	119 (62.6)		
Type of delivery				
Vaginal	178 (77.1%)	143 (75.3%)	0.91 (0.58-1.42)	0.667[c]
Cesarean section	53 (22.9%)	47 (24.7%)	1	
Professional who attended the delivery				
Doctor	151 (65.4%)	145 (76.3%)	1	0.065[c]
Nurse	66 (28.6%)	35 (18.4%)	1.81 (1.13-2.89)	
Multiprofessional team	12 (5.2%)	7 (3.7%)	1.65 (0.63-4.30)	
No information	2 (0.9%)	3 (1.6%)	0.64 (0.11-3.89)	
Robson's classification				
1	118 (51.1)	111 (58.4)	1	0.95[d]
2	12 (5.2)	3 (1.6)	3.76 (1.03-13.89)	
3	69 (29.9)	62 (32.6)	4.70 (0.54-40.89)	
4	5 (2.2)	1 (0.5)	1.05 (0.68-1.61)	
5	24 (10.4)	12 (6.3)	1.88 (0.89-3.94)	
6	2 (0.9)	1 (0.5)	1.88 (0.17-21.04)	
7	1 (0.4)	0 (0)	*	

PR: Prevalence ratio, CI: Confidence interval, [c]chi-square Pearson test, [d]Fisher's exact test; *Impossible to calculate

first five groups of the Robson classification, 0.9% in groups 6 and 7 and none of them in the groups 8, 9 and 10.

Table 2 shows that during the evening and at night, maternal morbidity was more prevalent, but was not significantly different when compared with that observed during the daytime. Maternal morbidity was low in both periods considered.

The mean labor duration was longer for cesarean section deliveries (13.8 hours) than the mean labor duration of vaginal deliveries (8.34 hours). The prevalence of cesarean section was not different between daytime and evening/nighttime births. Among the cesarean sections, the main indications were fetal distress (29%), cephalopelvic disproportion (28%), functional dystocia (22%), and ≥2 previous cesarean sections (19%).

Table 3 shows the perinatal outcomes. Neonatal infection was more frequent in deliveries that took place in the evening and during the night (PR: 2.11). There was no difference in Apgar scores, need for oxygen, need for resuscitation, or jaundice. A greater number of hospitalizations in the neonatal ICU (PR: 2.99) were observed during the evening and at nighttime.

Multivariate analysis did not show any statistical difference between the analyzed data. Infection and admission at ICU were the factors that showed association with the delivery shift in the univariate analysis. Comparison between the two groups for the variable "number of previous cesarean sections" resulted in a $p<0.2$, which could suggest some interaction with the delivery type. However on univariate analysis history of previous cesarean section was shown to have had no influence on the results (Table 4).

Multivariate analysis was performed for outcomes that were shown to be statistically different between the shifts in which the birth occurred. Multivariate analyses for the outcomes of infection, admission of the newborn, type of delivery and presence of previous cesarean section are shown in Table 4, 5. When performing the analysis, the outcome of infection and admission of the newborn did not show statistically significant association, and neither did the delivery shift or previous cesarean section.

Discussion

It is encouraging that among the main results found, there was an absence of difference in maternal morbidity between delivery times. While newborns at evening/night-time had a higher prevalence of infection and hospitalization in the ICU, there was no significance differences for other perinatal morbidities.

The difficulty of accessing the patients' medical records, due to logistical issues and the retrospective design, together with

Table 2. Maternal morbidity according to the birth time

	Day	Evening/night		
Variable	**n (%)**	**n (%)**	**PR (CI 95%)**	**p[d]**
	231 (100.0)	**190 (100.0)**		
Severe bleeding				
No	230 (99.6)	188 (98.9)	2.44 (0.22-27.19)	0.466
Yes	1 (0.4)	2 (1.1)		
Blood transfusion				
No	230 (99.6)	188 (98.9)	2.44 (0.22-27.19)	0.466
Yes	1 (0.4)	2 (1.1)		
Puerperal infection				
No	228 (98.7)	184 (96.8)	2.47 (0.61-10.04)	0.204
Yes	3 (1.3)	6 (3.2)		
Hysterectomy				
No	231 (100.0)	189 (99.5)	-	0.451
Yes	0 (0.0)	1 (0.5)		
Uterine rupture				
No	231 (100.0)	190 (100.0)	-	-
Yes	0 (0.0)	0 (0.0)		
Admission at ICU				
No	230 (99.6)	189 (99.5)	1.21 (0.07-19.58)	0.890
Yes	1 (0.4)	1 (0.5)		

ICU: Intensive care unit, PR: Prevalence ratio, CI: Confidence interval, [d]Fisher's exact test

data being collected from secondary sources are limitations of the study.

Evening and night-time deliveries are associated with increased perinatal mortality and adverse perinatal outcomes. Gijsen et al. (7) observed that there was a higher risk of adverse perinatal outcomes among evening/night-time deliveries, regardless of whether the pregnant woman was in the hospital before the delivery or she was referred during labor, and proposed that newborns who were delivered during the evening and night-time may have been exposed to a longer first phase of labor and were thus at higher risk of adverse perinatal outcomes. These results can be compared to the current study which showed lower Apgar scores at the 1st and 5th minute, a higher prevalence of newborns admitted to the neonatal ICU and infection when delivered during the evening/night-time. Hospitalization in the ICU was likely related to the higher risk of infection presented by these newborns. No significant difference was observed regarding the need to use oxygen and resuscitation in the delivery room when comparing birth shifts. In the present study, evening/night-time deliveries were associated with puerperal infection, hysterectomy and need for admission to the ICU. Lyndon et al. (8) corroborate these findings, since they identified that severe morbidity from heart failure, severe postpartum hemorrhage, and sepsis were associated with evening and nighttime deliveries. These authors demonstrated that evening and nighttime delivery is a risk factor for maternal morbidity, regardless of other obstetric and sociodemographic risk factors, such as cesarean section, race, and education (8).

Table 3. Perinatal outcomes according to the birth time

	Day	**Evening/night**		
Variable	**n (%)**	**n (%)**	**PR (CI 95%)**	**p**
	231 (100.0)	**190 (100.0)**		
Birthweight				
2,501-3,500 g	171 (74%)	129 (67.9%)	0.74 (0.49-1.13)	0.167[c]
3,501-4,499 g	60 (26%)	61 (32.1%)	-	
Apgar score at 1st min				
<7	15 (6.5)	14 (7.4)	0.87 (0.41-1.86)	0.724[c]
≥7	216 (93.5)	176 (92.6)		
Apgar score at 5th min				
<7	1 (0.4)	2 (1.1)	0.4 (0.04-4.54)	0.466[d]
≥7	230 (99.6)	188 (98.9)		
Need for oxygen				
No	199 (86.1)	162 (85.7)	1.03 (0.59-1.80)	0.899[c]
Yes	32 (13.9)	27 (14.3)		
Resuscitation at delivery room				
No	220 (95.7)	179 (94.7)	1.23 (0.50-3.01)	0.653[c]
Yes	10 (4.3)	10 (5.3)		
Admission of newborn				
Joint accommodation	207 (89.6)	141 (74.2)	2.99 (1.76-5.10)	<0.001[c]
Intensive care unit	24 (10.4)	49 (25.8)		
Jaundice				
No	82 (35.5)	62 (32.8)	1.12 (0.75-1.69)	0.563[c]
Yes	149 (64.5)	127 (67.2)	-	-
Infection				
No	211 (92.1)	161 (84.7)	2.11 (1.13-3.93)	0.019[c]
Yes	18 (7.9)	29 (15.3)		
Blood transfusion				
No	230 (99.6)	188 (98.9)	2.44 (0.22-27.19)	0.466[d]
Yes	1 (0.4)	2 (1.1)		

PR: Prevalence ratio, CI: Confidence interval, [c]Pearson's chi-square test, [d]Fisher's exact test

Bell et al. (9) analyzed the impact of birth during the evening/night-time in the context of maternal or perinatal morbidity and mortality and observed that pregnant women who gave birth during the evening or at night-time were less likely to have hypertension or pre-eclampsia and were less likely to require cesarean section delivery. Conversely, a higher percentage of women who gave birth at the end of the night presented with antepartum hemorrhage and evening and night-time deliveries were associated with lower Apgar scores.

Mgaya et al. (10) observed that deliveries during the evening/night-time were associated with a higher proportion of adverse perinatal outcomes, including low Apgar scores, fetal distress, early and neonatal death, and stillborn cases. We did not register any maternal or neonatal deaths during the different delivery times. Births at night, weekends and holidays are associated with a higher rate of unfavorable umbilical artery pH indices, with pH values <7.10 and Apgar scores <5 at 5 minutes (11). The objective of this study was not to evaluate the pH results of umbilical cord blood, as it is not routine in our service. However such data is an important indicator of the condition of the fetus at birth.

Aiken et al. (12) reported no differences in the risk of adverse perinatal outcomes between deliveries that were carried out during the day and those that were carried out in the evening or at night. However, they suggested that the number of hours already worked by clinical staff before providing assistance for unscheduled deliveries significantly influenced the risk of adverse perinatal outcomes. In an Irish study in 2014, deliveries at a tertiary obstetric unit that occurred at night were associated with a potential increase in rates of adverse maternal and neonatal outcomes. However, they did not identify a difference in birth weight in babies during the two periods, and when examining the mode of delivery, they found that women who gave birth at night were less likely to do so by caesarean section. Hehir et al. (13) in 2014 suggested that maternal and neonatal complications may occur at night due to the reduced number of staff and, in keeping with the report of Aiken et al. (12), fatigue, which may interfere with decision making and management of patients. Fatigue generated by long hours of work before taking a shift in a maternity ward, excessive hours of work, and excessive responsibility for parturients generated by the reduced number of health professionals, especially at night-time, seem to interfere in decision-making and quality of care provided, relating to possible adverse maternal and perinatal outcomes. Policy makers should ensure there is adequate financial and systemic support for the allocation of human resources and increase the provision of labor facilities in vulnerable areas, in addition to increasing staff numbers during the weekends or night-time to improve the quality of maternal intra- and post-delivery care (14).

The institution where the research was undertaken is considered a reference for good practices in care and birth, in addition to receiving higher risk patients from all municipalities in the state. This results in a large number of current births, on average 4,100 annually, suggesting that the findings can be extrapolated to the local population, although it should be borne in mind that a higher proportion of difficult deliveries is likely in the current cohort.

The findings of this study demonstrate that births occurring during the night shift were related to adverse neonatal outcomes. This data demonstrates the need for institutional assistance for the newborn and, perhaps, a need for an assessment of the performance of existing routines. There is the possibility that these results are replicated in other institutions, and it is important to highlight the necessary care standards regardless of the time of the assistance provided. These results also highlight the importance of training so that standardized practices are available. We believe that there should be further studies, which may identify factors affecting the quality of the assistance provided, in order to optimize delivery assistance and which would result in excellent service provision, with the least possible error.

Table 4. Multivariate analysis

Predictor	CI 95%	Odds ratio	p
Admission of newborn			
Joint accommodation Intensive care unit	0.9523-3.925	1.9333	0.068
Delivery shift			
Evening/night-day	0.9943-3.580	1.8866	0.052
Previous cesarean sections			
Yes-No	0.3166-2.945	0.9656	0.951
Estimates represent the log odds of infection = Yes vs Infection = No. CI: Confidence interval			

Table 5. Multivariate analysis

Predictor	CI 95%	Odds ratio	p
Delivery shift			
Evening/night-day	0.9943-3.580	1.8866	0.052
Admission of newborn			
Joint accommodation Intensive care unit	0.9523-3.925	1.9333	0.068
Previous cesarean sections			
Yes-No	0.3166-2.945	0.9656	0.951
Estimates represent the log odds of infection = Yes vs Infection= No. CI: Confidence interval			

The present study did not receive external funding and the authors declare that there is no conflict of interest that could constitute an impediment to the publication of this article.

Conclusion

Evening/night-time births were not associated with adverse maternal outcomes. However, a higher prevalence of adverse neonatal outcomes, in particular infection and requirement for ICU admission, were found in neonates delivered in the evening/night-time period.

Ethics Committee Approval: *The research complied with resolution no 466/2012 of the National Health Council and was approved by the local ethics committee (approval number: 957,050).*

Informed Consent: *It was obtained.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Surgical and Medical Practices: J.A.F.M.A.; Concept: C.R.P.M.V., F.H.C.C.; Design: C.R.P.M.V.; Data Collection or Processing: M.Q.M.; Analysis or Interpretation: F.H.C.C.; Literature Search: J.A.F.M.A.; Writing: E.A.J., F.H.C.C.*

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

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

References

1. Shakibazadeh E, Namadian M, Bohren MA, Vogel JP, Rashidian A, Nogueira Pileggi V, et al. Respectful care during childbirth in health facilities globally: a qualitative evidence synthesis. BJOG 2018; 125: 932-42.
2. Alvares AS, Corrêa ÁCP, Nakagawa JTT, Teixeira RC, Nicolini AB, Medeiros RMK. Humanized practices of obstetric nurses: contributions in maternal welfare. Rev Bras Enferm 2018; 71(suppl 6): 2620-7.
3. Pereira RM, Fonseca GO, Pereira ACCC, Gonçalves GA, Mafra RA. [New childbirth practices and the challenges for the humanization of health care in southern and southeastern Brazil]. Cien Saude Colet 2018; 23: 3517-24.
4. Hamilton P, Restrepo E. Weekend birth and higher neonatal mortality: a problem of patient acuity or quality of care? J Obstet Gynecol Neonatal Nurs 2003; 32: 724-33.
5. Wu YW, Pham TN, Danielsen B, Towner D, Smith L, Johnston SC. Nighttime delivery and risk of neonatal encephalopathy. Am J Obstet Gynecol 2011; 204: 37.e1-6.
6. de Graaf JP, Ravelli AC, Visser GH, Hukkelhoven C, Tong WH, Bonsel GJ, et al. Increased adverse perinatal outcome of hospital delivery at night. BJOG 2010; 117: 1098-107.
7. Gijsen R, Hukkelhoven CW, Schipper CM, Ogbu UC, de Bruin-Kooistra M, Westert GP. Effects of hospital delivery during off-hours on perinatal outcome in several subgroups: a retrospective cohort study. BMC Pregnancy Childbirth 2012; 12: 92.
8. Lyndon A, Lee HC, Gay C, Gilbert WM, Gould JB, Lee KA. Effect of time of birth on maternal morbidity during childbirth hospitalization in Californi. Am J Obstet Gynecol. 2015; 213: 705.e1-11.
9. Bell EF, Hansen NI, Morriss FH Jr, Stoll BJ, Ambalavanan N, Gould JB, et al. Impact of timing of birth and resident duty-hour restrictions on outcomes for small preterm infants. Pediatrics 2010; 126: 222-31.
10. Mgaya A, Hinju J, Kidanto H. Is time of birth a predictor of adverse perinatal outcome? A hospital-based cross-sectional study in a low-resource setting, Tanzania. BMC Pregnancy Childbirth 2017; 17: 184.
11. David M, Henrich W, Schlembach D, Lanowska M, Razum O, Breckenkamp J. Is There a Negative Night or Weekend Effect on the Child's Postnatal State Among Migrant Women? Z Geburtshilfe Neonatol 2020; 224: 143-9.
12. Aiken CE, Aiken AR, Scott JG, Brockelsby JC. The influence of hours worked prior to delivery on maternal and neonatal outcomes: a retrospective cohort study. Am J Obstet Gynecol 2016; 215: 634.e1-634.e7.
13. Hehir MP, Walsh JM, Higgins S, Mahony R. Maternal and neonatal morbidity during off peak hours in a busy obstetric unit. Are deliveries after midnight more complicated? Acta Obstet Gynecol Scand 2014; 93: 189-93.
14. Nam JY, Lee SG, Nam CM, Park S, Jang SI, Park EC. The effect of off-hour delivery on severe maternal morbidity: a population-based cohort study. Eur J Public Health 2019; 29: 1031-6.

Placenta percreta - a management dilemma: an institutional experience and review of the literature

Kavita Khoiwal[1], Amrita Gaurav[1], Dhriti Kapur[1], Om Kumari[1], Pankaj Sharma[2], Rekha Bhandari[3], Jaya Chaturvedi[1]

[1]Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, Rishikesh, India
[2]Department of Radiology, All India Institute of Medical Sciences, Rishikesh, India
[3]Department of Pathology, All India Institute of Medical Sciences, Rishikesh, India

Abstract

Objective: Placenta percreta is an extremely high-risk obstetric condition often associated with significant maternal morbidity and mortality. To date, there is no consensus on its management. This article aimed to identify an optimum management option to improve maternal outcomes in patients with placenta percreta.

Material and Methods: This was an observational study conducted at a tertiary care institute from October 2019 to June 2020. A well-defined plan of preoperative, bilateral, uterine artery catheter placement, cesarean delivery (CD) of the baby followed by uterine artery embolization (UAE), and elective delayed hysterectomy after 2-4 weeks, was made by a multidisciplinary team. Demographic variables such as age, parity, period of gestation, presenting complaints, imaging findings, mode of management, intraoperative findings, blood loss, the requirement for blood and blood products, and complications were noted.

Results: We encountered seven cases of placenta percreta over a period of nine months. UAE was performed in 6/7 patients. UAE was not performed in one patient as she presented to the emergency department in shock. Elective delayed hysterectomy was performed after 2-4 weeks in three patients, three patients required emergency hysterectomy (two during CD and one on the seventh postoperative day) and one patient was managed conservatively by leaving the placenta in situ after CD and UAE. Patients who underwent UAE had notably less intraoperative blood loss and requirement of blood and blood products than the patient who could not receive UAE. During cesarean hysterectomy, blood loss was 1,700 mL in embolized (case 4) vs 3,000 mL in unembolized patient (case 7). In embolized patients, the median blood loss during CD (case 1,2,3,5,6) was 200 mL (interquartile range: 165-200 mL) and during delayed elective hysterectomy (case 1,3,5) was 150 mL (range: 125-225 mL). Blood loss in case 2 was 1,000 mL during emergency hysterectomy on the 7th day of CD and UAE. The blood loss was appreciably higher in patients who underwent immediate cesarean hysterectomy rather than elective delayed hysterectomy.

Conclusion: Placenta percreta, if not managed in a preplanned manner, may lead to disastrous maternal outcomes. Prophylactic devascularization during CD and leaving the placenta in situ followed by elective delayed hysterectomy, might be a reasonable management option in most severe cases of placenta percreta. (J Turk Ger Gynecol Assoc 2020; 21: 228-35)

Keywords: Placenta percreta, uterine artery embolization, elective delayed hysterectomy, immediate cesarean hysterectomy

Received: 22 June, 2020 **Accepted:** 13 October, 2020

Introduction

Placenta percreta is one of the most dreaded obstetric complications. The overall incidence of placenta percreta is low at 5% of all placenta accreta spectrum (PAS) cases, but the incidence is currently rising owing to an increased rate of cesarean deliveries (CD). The reported incidence of PAS is 1 in 300 (1) and the risk of bladder invasion is much lower (1 in 10,000 pregnancies) (2). PAS is associated with significant maternal morbidity (24-67%) including intractable hem-orrhage (2-4 liters), bladder injury, a requirement for massive blood transfusion, disseminated intravascular coagulopathy (DIC), thromboembolism, systemic infection, sometimes repeat surgeries (3) and mortality (7%) (4). The severity of complications

Address for Correspondence: *Kavita Khoiwal*
e.mail: kavita.kh27@gmail.com ORCID: orcid.org/0000-0002-3156-7486

Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2020.2020.0106

increases with the severity of placental invasion. Therefore, placenta percreta is the most dangerous manifestation of PAS.

To date, there is no consensus on the management of these cases. However, cesarean hysterectomy is the widely accepted management for PAS (5). In contrast, a conservative management option includes leaving the placenta in situ for spontaneous resorption, but it is associated with increased morbidity, high risk of infection, hemorrhage, and a requirement for emergency hysterectomy in 58% of cases within nine months of cesarean section (6). Moreover, in cases of placenta percreta, owing to the high morbidity and mortality rate, it seems reasonable to utilize alternative options such as delayed hysterectomy with or without prophylactic devascularization (7). The debate continues between a conservative or surgical approach, and immediate cesarean hysterectomy or elective delayed hysterectomy.

We report a series of seven cases of placenta percreta managed successfully at our institute. The aim was to identify an optimum management option to improve maternal outcomes in patients with placenta percreta based on the available literature.

Material and Methods

This was an observational study conducted at the department of obstetrics and gynaecology of a tertiary care institute. Being a referral center and despite the low prevalence, seven cases of placenta percreta were encountered over a period of nine months, from October 2019 to June 2020. All cases in which the placenta was found to be invading the entire uterine wall, penetrating the uterine serosa, and encroaching adjacent organs, such as the bladder or parametrium were designated placenta percreta. The initial method of diagnosis of placenta percreta was ultrasound (USG), subsequently confirmed with magnetic resonance imaging (MRI).

On referral of the first case, a multidisciplinary team including a senior obstetrician, interventional radiologist, urologist, transfusion medicine, neonatologist, critical care, and anesthetist was formed to avoid or minimize intraoperative hemorrhage and postoperative complications. After thorough discussion of the pros and cons of the conservative and surgical approach, a well-defined plan of preoperative bilateral uterine artery catheter placement, CD of the baby followed by uterine artery embolization (UAE) and elective delayed hysterectomy after 2-4 weeks (Figure 1) was formed. A transverse incision on the uterine fundus was planned to deliver the baby during cesarean section, as lower segment transverse or vertical incision can directly transect the placenta (8). Similarly, a vertical incision over the upper uterine segment may extend to the placental margins and lead to catastrophic hemorrhage, resulting in increased maternal-fetal morbidity and mortality.

A written and informed consent was taken from all patients. The study was reviewed and approved by the Institutional Ethical Committee (approval number: AIIMS/IEC/20/341) of All India Institute of Medical Sciences Rishikesh.

Antenatal booking status, referral, demographic variables such as age, parity, period of gestation, presenting complaints, imaging findings, mode of management, intraoperative findings, blood loss, a requirement of blood and blood products, and complications were noted.

Statistical analysis

Baseline demographic characteristics, intraoperative, and postoperative outcome variables of all cases of placenta percreta were noted in a tabular form. Descriptive statistics were used to calculate simple frequency, percentage, and proportion. Intraoperative blood loss was calculated as median with interquartile range.

Results

Table 1 shows baseline demographic characteristics, imaging, and intra-operative and post-operative variables. All patients

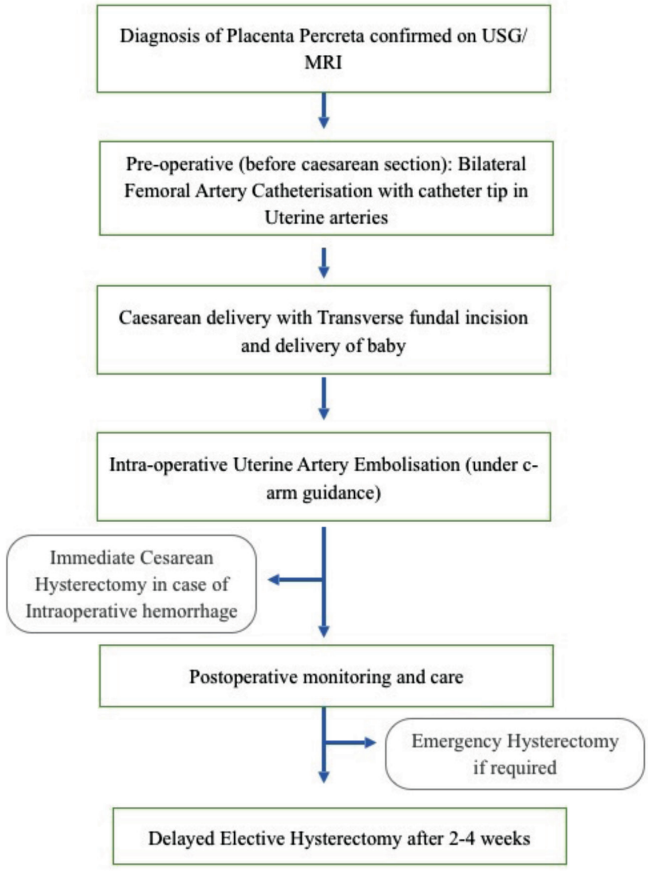


Figure 1. Algorithm for management of placenta percreta at our centre

USG: Ultrasound, MRI: Magnetic resonance imaging

Table 1. Baseline demographic characteristics, intraoperative, and postoperative outcome variables of placenta percreta cases

S. No.	Age	Parity & previous history of CD	Booking status	Presenting complaint	Imaging (MRI)	UAE	Primary procedure	Intra-operative findings	Final mode of management	Complications	Intraoperative blood loss	Requirement of BT
1	34	G3P2L2 Previous 2 CD	Unbooked	Referred in view of placenta percreta	Placenta percreta with bladder invasion (Figure 2)	Yes	Elective cesarean at 37 weeks POG; with intra-operative UAE after CD	Placenta percreta involving the bladder (Figure 3a)	Elective hysterectomy on day 14	None	CD: 200 mL, hysterectomy: 150 mL	-
2	30	G6P5L3 Previous 3 CD	Unbooked	Presented at 33 weeks with one episode of APH	Central placenta previa with placenta percreta	Yes	Elective cesarean at 35+3 weeks POG with intra-operative UAE after CD	Placenta percreta involving posterior wall of uterus (Figure 3b)	Emergency hysterectomy on day 7 in view of PPH	PPH	CD: 180 mL, hysterectomy: 1000 mL	2 units of PRBC
3	34	G8P3L3A4 Previous 3 CD	Unbooked	Referred in view of placenta percreta	Placenta percreta	Yes	Elective cesarean at 34+5 weeks POG with intraoperative UAE after CD	Placenta percreta extending anteriorly up to bladder serosa	Elective hysterectomy on day 14	None	CD: 150 mL, hysterectomy: 125 mL	-
4	34	G3P2L1 Previous 2 CD	Unbooked	Presented at 33+4 weeks with pain abdomen	Placenta previa with features of percreta	Yes	Emergency cesarean at 34 weeks POG in view of preterm labor; with intraoperative UAE after CD	Placenta percreta invading anteriorly, bladder densely adhered	Immediate cesarean hysterectomy	Massive intraoperative hemorrhage from placental sinuses	Cesarean hysterectomy: 1.700 mL	3-unit PRBC
5	34	G4P3L3 Previous 1 CD	Booked	Admitted at 34+4 weeks with pelvic heaviness	Placenta percreta involving dome of urinary bladder	Yes	Elective cesarean at 35+3 weeks POG with intraoperative UAE after CD	Placenta percreta, bulging out anteriorly	Elective hysterectomy on day 30	None	CD: 200 mL, hysterectomy: 225 mL	-
6	29	G4P3L2 Previous 3 CD	Booked	Admitted at 34 weeks for safe confinement	Placenta percreta	Yes	Elective cesarean at 35 weeks POG with intraoperative UAE after CD	Placenta percreta, bulging out anteriorly	Conservative management, on follow up for last 4 months; placenta regressing in size	None	CD: 200 mL	-

Table 1. Continued

S. No.	Age	Parity & previous history of CD	Booking status	Presenting complaint	Imaging (MRI)	UAE	Primary procedure	Intra-operative findings	Final mode of management	Complications	Intraoperative blood loss	Requirement of BT
7	30	G5P2L2A2 Previous 2 CD	Unbooked	Presented in emergency with APH	USG: Central placenta previa with suspicion of adherent placenta	No	Emergency CD at 37 weeks POG; with cesarean hysterectomy	Placenta was densely adhered and invaded posterior surface of uterus	Cesarean hysterectomy in view of uncontrolled hemorrhage even after stepwise devascularisation	Massive intraoperative hemorrhage, patient kept in critical care unit for 2 days	Cesarean hysterectomy: 3,000 mL	6-unit PRBC, 4 RDP, and 4 FFP

UAE: Uterine artery embolization, POG: Period of gestation, CD: Cesarean delivery; APH: Antepartum hemorrhage, PPH: Postpartum hemorrhage, PRBC: Packed red blood cells, RDP: Random donor platelets, FFP: Fresh frozen plasma, MRI: Magnetic resonance imaging, USG: Ultrasound, BT: Blood transfusion

were young, with age ranging from 29 to 34 years. Most of the patients (5/7) were unbooked and either referred or presented to the emergency department. Planned elective CDs were performed at 34-36 weeks of gestation, with the exceptions of case 1 and case 7 when CD was performed at approximately 37 weeks, as they presented in late gestation (Table 1). Figure 2 shows MRI and cystoscopic image of case 1.

UAE was performed in 6/7 (85.7%) patients as per our protocol. On the day of CD, bilateral femoral arteries were catheterized, with catheter tips placed bilaterally on uterine arteries under USG guidance. The patient was then shifted to the operating theatre for CD. General anesthesia was administered, and the abdomen opened in layers under asepsis. Intraoperative findings of case 1 and case 2 are shown in Figure 3. A transverse fundal incision was made to deliver the baby, cord clamped, and cut. No oxytocics were given. Signs of spontaneous placental separation were awaited. In the absence of such signs the placenta was left in situ. Then the interventional radiologist, in the operating theatre itself, confirmed the position of catheter tips on bilateral uterine arteries under C-arm guidance with subsequent embolization with gel foam until stasis was achieved. Case 4 required immediate cesarean

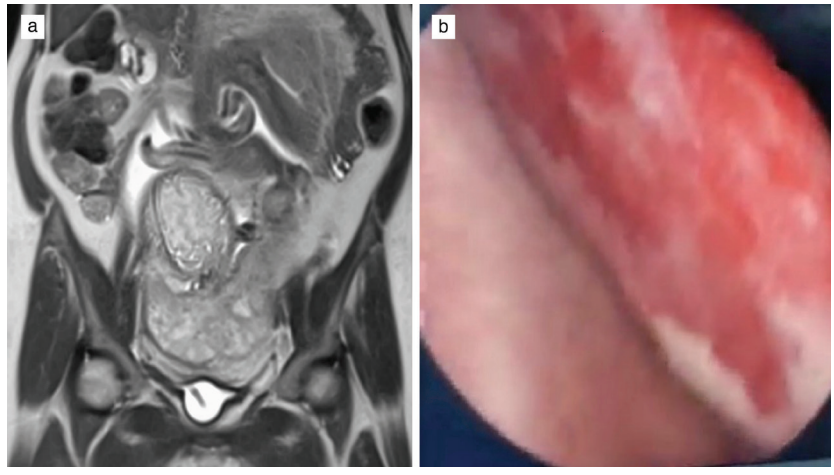


Figure 2. (a) T2 weighted magnetic resonance imaging (coronal section) showing placenta invading through the lower uterine segment reaching up to bladder serosa; (b) Cystoscopy showing placental bulge with intact bladder mucosa

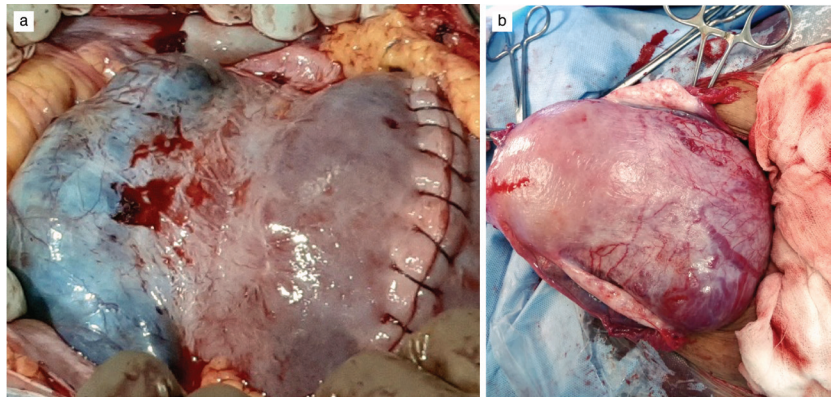


Figure 3. Intraoperative image of showing placenta percreta with an anterior bulge in case 1 (a) and a posterior bulge in case 2 (b)

hysterectomy because of massive hemorrhage from placental sinuses. In all other cases, after ensuring that there was no bleeding from the placental site and vagina, the uterus was closed followed by the abdomen. All surgeries were performed by the same surgeons.

Every patient was closely observed in the post-operative period. Case 2 developed significant postpartum hemorrhage (PPH) on the seventh day after surgery and was taken for emergency hysterectomy during which no intraoperative complications were faced. Elective delayed hysterectomy was successfully performed on the 14th day in cases 1 and 3 and on the 30th day of CD in case 5. Case 6 was keen for conservative management and has thus been kept on regular follow up for the last four months. Her USG suggested a regressed placenta.

UAE could not be performed in case 7 as she presented to the emergency department at midnight with antepartum hemorrhage and features of shock. Therefore, she was immediately taken for cesarean hysterectomy. Intraoperative blood loss was significant (approximately 3,000 mL) and required more than four units of packed red blood cells. In comparison, blood loss during immediate cesarean hysterectomy in an embolized patient (case 4) was 1,700 mL.

In embolized patients (cases 1,2,3,5,6), the median (interquartile range) blood loss during CD was 200 (165-200) mL and during delayed elective hysterectomy (case 1,3,5) was 150 (range: 125-225 mL). Blood loss in case 2 was 1,000 mL during emergency hysterectomy on the seventh day after CD and UAE. Intraoperative blood loss and requirement for blood and blood products are shown in Table 1.

Figure 4 shows uterine specimens of cases 1 and 2 at the time of delayed hysterectomy, significantly regressed in size and vascularity. All seven patients did well in their postoperative period. The final diagnosis of percreta was confirmed by histopathology. Figure 5 shows the histopathological image of case 1.

Using this planned multidisciplinary team approach, a good maternal and fetal outcome was achieved.

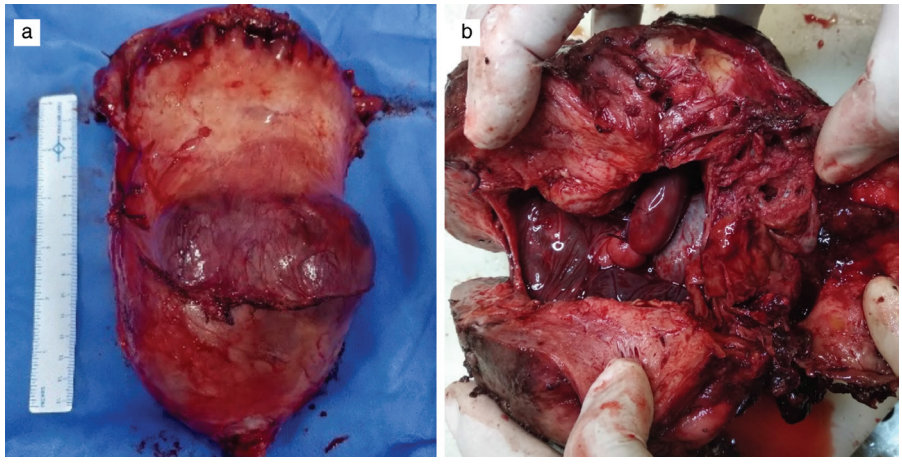


Figure 4. Hysterectomy specimen showing placenta percreta in case 1 (a) and 2 (b)

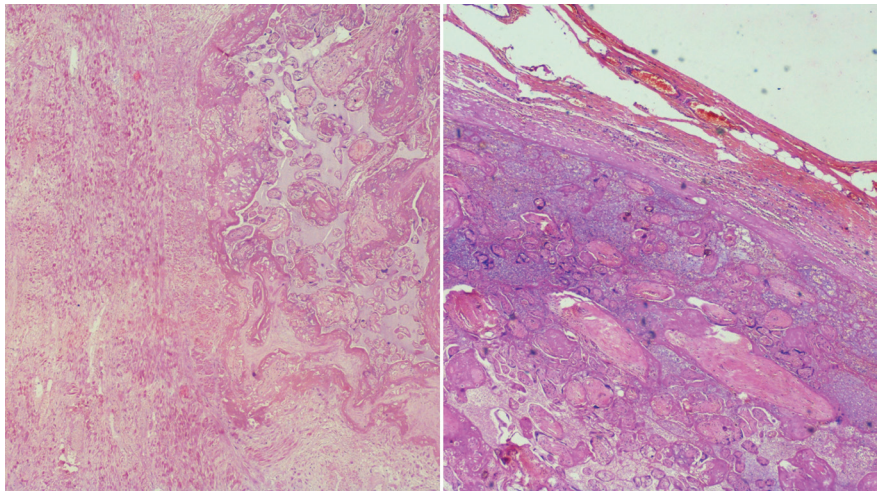


Figure 5. Hematoxylin and eosin (40x) stained sections of case 1, showing chorionic villi implanted into the myometrium without intervening decidua and full thickness invasion of the myometrium

Discussion

The optimal management of placenta percreta is not yet clear. A wide array of management options have been discussed in the literature, yet no preferred management modality has been identified, possibly due to the low incidence of such cases. There is an ongoing debate whether to go for cesarean hysterectomy or conservative management leaving placenta in situ with or without elective delayed hysterectomy.

Cesarean hysterectomy in cases of placenta percreta is associated with high rates of severe maternal morbidity (40-50%) and mortality (7%) (7). Similarly, high maternal morbidity (56%) during conservative management of placenta percreta has been reported by Matsuzaki et al. (9) in a systemic review. Massive hemorrhage and urinary tract injury are the most worrisome complications of cesarean hysterectomy, whereas the conservative approach is associated with late complications of leaving the placenta in situ. These late complications include secondary PPH, infection, DIC and need for an emergency hysterectomy (10). Therefore, detailed counseling of the patients, informed consent, and multidisciplinary approach for management is mandatory in these cases for an optimum outcome. We performed delayed hysterectomy wherever feasible, to avoid complications related to both approaches. Delaying hysterectomy might result in decreased uterine blood flow and regression of placenta from surrounding structures. UAE was also performed in most of the cases to minimize hemorrhage.

The exact time to perform delayed hysterectomy is debatable. The timing of elective delayed hysterectomy in our study was after 2-4 weeks following CD. In contrast, Zuckerwise et al. (7) suggested that the ideal time for hysterectomy was after 4-6 weeks subsequent to CD. However, Collins et al. (11) suggested re-evaluation of the time of delayed hysterectomy as they hypothesized that if the patient remains stable after 4-6 weeks of CD, hysterectomy may not be needed. The International Society for Abnormally Invasive Placenta also documented no added advantage of elective delayed hysterectomy, and the associated potential risks of a second elective surgery in a stable patient (12). Similarly, Matsuzaki et al. (13) reported spontaneous placental absorption in 80% of cases after 4-6 weeks of CD during a conservative approach and suggested that elective hysterectomy may not be required after 4-6 weeks of CD. However, 10% of conservatively managed cases had a massive hemorrhage, and 10% of cases developed fistula formation, arteriovenous malformation, and DIC leading to emergency hysterectomy (13). Hence, the questions "whether to plan for elective delayed hysterectomy or not" and "when" are still unanswered.

In our experience, patients who underwent planned elective surgery had lesser blood loss and morbidity than emergency surgery. Silver et al. (14) also documented better maternal outcomes with elective surgeries.

We experienced appreciably higher blood loss in patients who underwent immediate cesarean hysterectomy compared to planned delayed hysterectomy. Likewise, Zuckerwise et al. (7) reported significantly high median estimated blood loss (EBL) with immediate hysterectomy (3,000 mL) compared to a delayed hysterectomy (1,300 mL) in placenta percreta cases. The requirement of transfusion of >4 units of RBC was also significantly higher in cases of immediate cesarean hysterectomy compared with delayed hysterectomy ($p=0.016$).

Ouerdiane et al. (15) in their prospective study on conservative management of placenta percreta, where no additional therapy was used, reported that almost 31% of cases were complicated by massive obstetric hemorrhage or infection and required an emergency hysterectomy. In such a scenario, the role of a conservative approach with additional procedures such as injection methotrexate and UAE to decrease vascularity may be considered as a safe management option. This further paves the way for a technically easier planned delayed hysterectomy with a reduced rate of peri- and post-operative complications. The efficacy of methotrexate is questionable in late pregnancy, as it acts only on proliferative cells and trophoblastic proliferation is absent in late pregnancy (16). Moreover, the adverse effects of the drug itself have led to discouragement in its use, whereas selective arterial embolization is reported to have a 90% success rate in cases of PAS disorders (17).

In our experience, patients who underwent UAE had a better outcome in terms of intraoperative blood loss and the requirement of blood and blood products. Although we had planned delayed hysterectomy from 2-4 weeks after CD and UAE, 2/6 patients required emergency hysterectomy. Nevertheless, the overall EBL was notably lower in them than the patient who could not receive UAE.

Wang et al. (18) also described significantly less EBL, need for blood transfusion, and length of ICU stay with UAE before hysterectomy than cesarean hysterectomy alone. On the contrary, Matsuzaki et al. (9) reported no benefit of prophylactic UAE to improve success rates, although they documented earlier placental resorption with UAE when compared to no UAE (22.4 weeks vs 35.3 weeks; $p=0.014$). Prophylactic devascularization, either surgically or radiologically, is expected to reduce intra-operative blood loss, secondary hemorrhage, and accelerate placental resorption (19,20).

Internal iliac artery balloon occlusion has also been found to minimize blood loss (21). Cali et al. (22) also documented a statistically significant reduction in mean EBL (933 vs 1507 cc). In contrast, Salim et al. (23) demonstrated no difference in mean EBL with internal iliac artery balloon occlusion in women undergoing CD for suspected PAS. In a review article, Kingdom

et al. (24) stated that with surgical expertise, balloon placement and devascularization do not improve patient outcomes. Additionally, it is highly demanding in terms of cost and hospital resources. Furthermore, vessel occlusion itself could pose certain complications such as hampered blood supply to lower limbs and pelvis (25), buttock necrosis (26), post embolization syndrome, uterine scarring, and secondary amenorrhea (27). We did not have any UAE-related complications in our case series.

Ligation of the anterior division of internal iliac arteries during surgery is another option although this is more surgically demanding. However, Hussein et al. (28) in a randomized trial reported no additional advantage of prophylactic internal iliac artery ligation during cesarean hysterectomy. It is well known that the blood supply of the lower uterine segment, para-vesical spaces, and vagina comes from both internal iliac arteries and collaterals of external iliac arteries in percreta cases. Kingdom et al. (24) further proposed a five step approach to cesarean hysterectomy which leads to a mean EBL of less than 1.5 liters.

In the literature review, other alternatives described to minimize intra-operative blood loss were balloon placement in the infra-renal aortic and common iliac arteries. Li et al. (29) did a retrospective study to compare outcomes of all three levels of balloons (infra-renal aortic, common iliac and anterior divisions of the internal iliac arteries) in women with suspected PAS and concluded that surgery with balloons placed in the infra-renal aorta or common iliac arteries had significantly lower mean blood loss (1,000 mL) than surgery with internal iliac artery balloons (2,900 mL) and significantly lower rates of hysterectomy.

The rationale behind prophylactic devascularization (UAE) in our cases was to minimize intraoperative hemorrhage and associated morbidity whereas delayed hysterectomy was performed to avoid late complications of placenta left in situ. Our approach aimed to obviate the drawbacks of both a conservative approach and primary cesarean hysterectomy. Given the fact that most of our patients had completed their family and were not eager for uterine conservation, we could use this combined approach to ensure the least morbid management. Furthermore, one of our patients wished to conserve her uterus and fortunately had no postoperative complications after CD and UAE. Embolization techniques can also be used with a conservative approach. However, the preference of management options should be individualized until we have a consensus on the optimum approach for management. We performed delayed hysterectomy 2-4 weeks after CD, which is quite early compared to other reports. A well-designed, multicentre, randomized, controlled trial with a large sample size is needed for further validation.

Conclusion

Placenta percreta, if not managed in a preplanned manner, may lead to disastrous maternal outcomes. Prophylactic devascularization along with cesarean delivery and leaving the placenta in situ, followed by elective delayed hysterectomy might be a reasonable management option in most severe cases of placenta percreta.

Ethics Committee Approval: *The study was reviewed and approved by the Institutional Ethical Committee (approval number: AIIMS/IEC/20/341) of All India Institute of Medical Sciences Rishikesh.*

Informed Consent: *A written and informed consent was taken from all patients.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Surgical and Medical Practices: K.K., A.G., O.K., D.K., P.S., R.B., J.C.; Concept: K.K., J.C.; Design: K.K., D.K., A.G.; Data Collection or Processing: K.K., D.K., O.K.; Analysis or Interpretation: K.K., D.K., P.S.; Literature Search: K.K., D.K.; Writing: K.K., D.K.*

Conflict of Interest: *All author's declare no conflict of interest.*

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

References

1. Morlando M, Sarno L, Napolitano R, Capone A, Tessitore G, Maruotti GM, et al. Placenta accreta: incidence and risk factors in an area with a particu-larly high rate of cesarean section. Acta Obstet Gynecol Scand 2013; 92: 457-60.
2. Miller DA, Chollet JA, Goodwin TM. Clinical risk factors for placenta previa-placenta accreta. Am J Obstet Gynecol 1997; 177: 210-4.
3. Royal College of Obstetricians and Gynecologists. Placenta Praevia and Placenta Accreta: Diagnosis and Management (Green-top Guideline No. 27a). London: RCOG; 2018.
4. Jauniaux E, Alfirevic Z, Bhide AG, Belfort MA, Burton GJ, Collins SL, et al. Placenta Praevia and Placenta Accreta: Diagnosis and Management: Green-top Guideline No. 27a. BJOG 2019; 126: e1-e48.
5. Cahill AG, Beigi R, Heine RP, Silver RM, Wax JR. Placenta accreta spectrum. Am J Obstet Gynecol 2018; 219: B2-16.
6. Clausen C, Lönn L, Langhoff-Roos J. Management of placenta percreta: a review of published cases. Acta Obstet Gynecol Scand 2014; 93: 138-43.
7. Zuckerwise L, Craig A, Newton J, Zhao S, Bennett K, Crispens M. Outcomes following a clinical algorithm allowing for delayed hysterectomy in the management of severe placenta accreta spectrum. Am J Obstet Gynecol 2020; 222: 179.e1-179.e9.
8. Kotsuji F, Nishijima K, Kurokawa T, Yoshida Y, Sekiya T, Banzai M, et al. Transverse uterine fundal incision for placenta praevia with accreta, in-volving the entire anterior uterine wall: a case series. BJOG 2013; 120: 1144-9.

9. Matsuzaki S, Yoshino K, Endo M, Kakigano A, Takiuchi T, Kimura T. Conservative management of placenta percreta. Int J Gynaecol Obstet 2018; 140: 299-306.
10. Luo G, Perni S, Jean-Pierre C, Baergen R, Predanic M. Failure of conservative management of placenta previa-percreta. J Perinat Med 2005; 33: 564-8.
11. Collins SL, Sentilhes L, Chantraine F, Jauniaux E. Delayed hysterectomy: a laparotomy too far? Am J Obstet Gynecol 2020; 222: 101-2.
12. Collins SL, Alemdar B, van Beekhuizen HJ, Bertholdt C, Braun T, Calda P, et al. Evidence-based guidelines for the management of abnormally inva-sive placenta: recommendations from the International Society for Abnormally Invasive Placenta. Am J Obstet Gynecol 2019; 220: 511-26.
13. Matsuzaki S, Grubbs BH, Matsuo K. Delayed hysterectomy versus continuing conservative management for placenta percreta: which is better? Am J Obstet Gynecol 2020; 223: 304.
14. Silver RM, Fox KA, Barton JR, Abuhamad AZ, Simhan H, Huls CK, et al. Center of excellence for placenta accreta. Am J Obstet Gynecol 2015; 212: 561-8.
15. Ouerdiane N, Daaloul W, Othmani K, Masmoudi A, Hamouda S, Bouguerra B. Conservative management of placenta percreta: tunisian prospective study. Gynecol Obstet Case Rep 2016; 2: 2.
16. Timmermans S, van Hof A, Duvekot J. Conservative management of abnormally invasive placentation. Obstet Gynecol Surv 2007; 62: 529-39.
17. Mei J, Wang Y, Zou B, Hou Y, Ma T, Chen M, et al. Systematic review of uterus-preserving treatment modalities for abnormally invasive placenta. J Obstet Gynaecol 2015; 35: 777-82.
18. Wang M, Ballah D, Wade A, Taylor AG, Rizzuto G, Li B, et al. Uterine artery embolization following cesarean delivery but prior to hysterectomy in the management of patients with invasive placenta. J Vasc Interv Radiol 2019; 30: 687-91.
19. Bouvier A, Sentilhes L, Thouveny F, Bouet PE, Gillard P, Willoteaux S, et al. Planned cesarean in the interventional radiology cath lab to enable immediate uterine artery embolization for the conservative treatment of placenta accreta. Clin Radiol 2012; 67: 1089-94.
20. Soyer P, Sirol M, Fargeaudou Y, Bour L, Morel O, Dohan A, et al. Placental vascularity and resorption delay after conservative management of inva-sive placenta: MR imaging evaluation. Eur Radiol 2013; 23: 262-71.
21. Petrov DA, Karlberg B, Singh K, Hartman M, Mittal PK. Perioperative internal iliac artery balloon occlusion, in the setting of placenta accreta and its variants: the role of the interventional radiologist. Curr Probl Diagn Radiol 2018; 47: 445-51.
22. Cali G, Forlani F, Giambanco L, Amico ML, Vallone M, Puccio G, et al. Prophylactic use of intravascular balloon catheters in women with placenta accreta, increta and percreta. Eur J Obstet Gynecol Reprod Biol 2014; 179: 36-41.
23. Salim R, Chulski A, Romano S, Garmi G, Rudin M, Shalev E. Precesarean prophylactic balloon catheters for suspected placenta accreta: a randomized controlled trial. Obstet Gynecol 2015; 126: 1022-8.
24. Kingdom JC, Hobson SR, Murji A, Allen L, Windrim RC, Lockhart E, et al. Minimizing surgical blood loss at cesarean hysterectomy for placenta previa with evidence of placenta increta or placenta percreta: the state of play in 2020. Am J Obstet Gynecol 2020; 223: 322-9.
25. Papillon-Smith J, Singh SS, Ziegler C. Internal iliac artery rupture caused by endovascular balloons in a woman with placenta percreta. J Obstet Gy-naecol Can 2016; 38: 1024-7.
26. Smith DD, Perez-Delboy A, Burke WM, Tergas AI. Buttock necrosis after uterine artery embolization for delayed hysterectomy in placenta percreta. Case Rep Obstet Gynecol 2016; 2016: 6921280.
27. Alanis M, Hurst B, Marshburn P, Matthews M. Conservative management of placenta increta with selective arterial embolization preserves future fertility and results in a favorable outcome in subsequent pregnancies. Fertil Steril 2006; 86: 1514.e3-7.
28. Hussein AM, Dakhly DMR, Raslan AN, Kamel A, Hafeez AA, Moussa M, et al. The role of prophylactic internal iliac artery ligation in abnormally invasive placenta undergoing cesarean hysterectomy: a randomized control trial. J Matern Fetal Neonatal Med 2019; 32: 3386-92.
29. Li K, Zou Y, Sun J, Wen H. Prophylactic balloon occlusion of internal 442 iliac arteries, common iliac arteries and infrarenal abdominal aorta in preg-nancies complicated by placenta accreta: a retrospective cohort study. Eur Radiol 2018; 28: 4959-67.

Outcomes of external cephalic version for antenatal women with breech presentation in a secondary hospital in Vellore, Tamil Nadu - a retrospective review

Tobey Ann Marcus[1], Shalini Jeyapaul[2], Sam Marconi David[2], Dimple Jamkhandi[3], Anne George Cherian[1]

[1]Department of Obstetrics and Gynaecology, Christian Medical College and Hospital, Vellore, India
[2]Department of Community Medicine, Christian Medical College and Hospital, Vellore, India
[3]Department of Family Medicine, Christian Medical College and Hospital, Vellore, India

Abstract

Objective: Breech presentation is the most common fetal malpresentation at term, with an incidence of 3-4%. External cephalic version (ECV) is a procedure that can be offered to women with breech presentation beyond 36 weeks of gestation to convert it to cephalic presentation, reducing the risks of a vaginal breech delivery and the morbidities associated with caesarean section.

Material and Methods: We retrospectively reviewed the records of women who underwent ECV between October 2012 and June 2020 with the objectives of determining the success rate of the procedure, the mode of delivery, the maternal and neonatal outcomes, periprocedural complications and their management.

Results: Among the 200 women who underwent the procedure with a 64% success rate (128 women), there were 110 vaginal deliveries (56.7%) including five vaginal breech deliveries, and 84 women (43.2%) underwent caesarean section, which included 24 women who had successful ECV but needed emergency caesarean for other indications. There was no significant difference in the neonatal APGAR scores in those who had a successful ECV and those who did not. Only three women (1.5%) experienced any significant periprocedural complication.

Conclusion: These results suggest that ECV improves the possibility of a vaginal delivery with an overall low complication rate, reducing the neonatal risks associated with vaginal breech delivery and the maternal morbidity of a caesarean section. It may thus contribute to reducing the primary caesarean section rate, making it a useful intervention, especially in limited resource settings. (J Turk Ger Gynecol Assoc 2020; 21: 236-42)

Keywords: Breech presentation, external cephalic version, limited resource setting

Received: 10 August, 2020 **Accepted:** 01 November, 2020

Introduction

Breech presentation is the most common fetal malpresentation with an incidence of about 3-4% at and near term (1). It could be secondary to a pre-existing maternal or fetal abnormality, or related to abnormal placentation, such as placenta praevia, cornual location of the placenta, or could also be a chance occurrence. Whatever the cause for the malpresentation, breech presentation is associated with an increased risk of either a complicated vaginal delivery with significant risk of perinatal morbidity or mortality, or a caesarean section which is accompanied by increased risk of maternal and fetal complications.

The term breech trial which was undertaken by Hannah et al. (2), reported a significantly decreased perinatal mortality and morbidity following planned caesarean section when compared to planned vaginal breech delivery. Following the publication of these results, a shift occurred in the management of breech presentation in labour, towards caesarean section with very few individuals and institutions being willing to take

Address for Correspondence: *Anne George Cherian*
e.mail: annegc97@yahoo.co.in ORCID: orcid.org/0000-0003-0751-3709

Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2020.2020.0140

risks with planned vaginal breech delivery. This resulted in an increase in the caesarean section rate for breech presentation to 95% internationally (3).

In a Cochrane review, published in 2003, comparing planned elective caesarean section with a trial of vaginal delivery for women with breech pregnancy at term, it was found that an elective caesarean section had increased maternal morbidity when compared to vaginal delivery. Furthermore, 45% of the women planned to have a trial of vaginal delivery eventually had an emergency caesarean section for another indication (4). Other studies have also shown that, although there is a minimal risk overall, the incidence of maternal mortality associated with planned caesarean section is higher than that of vaginal birth (5,6). Apart from the increased risk of morbidity and mortality in the index pregnancy, caesarean delivery also poses significant risks for subsequent pregnancies, including the possibility of placenta praevia and morbidly adherent placenta. Another factor against advocating universal elective caesarean delivery for breech presentation is that the procedure requires the expertise of an obstetrician or another surgically trained health worker. This limits the role of low-risk obstetric health workers like midwives and general practitioners.

A review of studies looking at strategies to reduce global caesarean section rates demonstrated that external cephalic version (ECV) was the only significant clinical intervention to reduce primary caesarean sections (7). However, despite these evidence-based benefits, it was found to be an underused procedure, resulting in a loss of skill over time in performing this procedure.

ECV is a procedure by which the singleton fetus is gently manipulated externally from a non-cephalic to a cephalic presentation. This is carried out after 36 weeks of gestation and usually after the administration of a tocolytic agent to relax the uterus. The purpose of this intervention is to decrease the incidence of breech presentation in labour and to decrease the maternal morbidity and mortality associated with caesarean delivery. The success rate of ECV is approximately 65% at term to convert non-cephalic into vertex presentation (8).

International societies of obstetrics and gynaecology have issued guidelines recommending the use of ECV in term antenatal women with the fetus in breech presentation. Absolute contra-indications to the procedure include multiple gestations, rupture of membranes, antepartum haemorrhage in the antecedent week, abnormal cardiotocography, the presence of uterine anomalies, fetal hyper-extended head and any other condition which otherwise warrants caesarean delivery, such as placenta praevia (9). In the absence of contra-indications, ECV should be offered to all women with a non-cephalic presentation beyond 36 weeks of gestation and should always be performed by skilled personnel (obstetrician or trained midwife).

The diagnosis of breech presentation on clinical examination during antenatal reviews is important because, in that event, the option of ECV can be considered and discussed with the patient. If a breech presentation is undiagnosed during the antenatal check-up, the woman usually presents in labour or with pre-labour rupture of membranes and in most cases is taken for emergency caesarean section, unless she is close to spontaneous vaginal breech delivery at the time of admission to the labour room.

This study was undertaken to investigate the feasability of ECV as an option in women with non-cephalic presentation at term, especially in a secondary hospital and other resource-limited settings, to avoid the neonatal morbidity associated with vaginal breech deliveries and the maternal and neonatal morbidity associated with caesarean delivery.

The objectives of this study were, firstly, to determine the success rate of ECV and the distribution of mode of delivery among women who underwent the procedure. Secondly, to study the delivery outcomes (maternal and neonatal) of women who had successful ECV and finally, to enumerate peri-procedural complications encountered and their management.

Material and Methods

This is a retrospective review of women who were diagnosed with breech presentation and underwent ECV at our hospital from October 2012 to May 2020. Clearance was obtained from The Institutional Review Board and Ethics Committee CMC Vellore, (IRB number: 11412). Informed consent couldn't be obtained in view of the retrospective nature of the study.

Setting

The study was based in a 140-bedded, secondary care level hospital, under the department of Community Health of a multidisciplinary tertiary care centre in South India. The hospital has been providing primary and secondary level maternal and child health services, focussing primarily on the residents of Kaniyambadi block, which is a rural development block in Vellore district, for the past 40 years. The services also extend to the surrounding areas of Vellore town as well as to residents of adjoining districts who wish to seek care at the hospital. Another area of primary focus is the tribal population of the Jawadhi hills which span over four panchayats in Vellore district and 11 in Thiruvanamalai district. Both out-patient and in-patient facilities are available at the hospital for different health conditions. The out-patient clinic includes both general services and speciality clinics for maternal and child health as well as communicable and non-communicable chronic diseases.

Obstetric services can be availed by anyone registered in the antenatal clinic at the base hospital or in the various mobile clinics that cater to the residents of Kaniyambadi block and the Jawadhi hills. The maternal health related services provided include a 24-hour labour room facility for normal and assisted delivery, operation theatre and caesarean sections under spinal anaesthesia. There is an established referral system to the department of obstetrics and gynaecology at the affiliated tertiary level centre. Data concerning deliveries, associated risk factors, and birth outcomes are recorded during pregnancy and childbirth in out-patient as well as in-patient records and entered into an electronic database. This electronic database with respect to both base hospital and community data has been maintained over the last 25 years.

In our hospital, ECV is offered to women with non-cephalic presentation at term in whom there are no contra-indications for vaginal delivery or for the procedure itself.

Time period

Over the last eight years (from 2012 onwards), a register has been maintained of women with breech presentation who underwent ECV. This record was used to retrieve information from the electronic database, of the outcomes of women who underwent the procedure from October 2012 to May 2020, including mode of delivery and condition of the baby at delivery.

Procedure

During the antenatal out-patient review, if a non-cephalic presentation was diagnosed at a gestational age of 36 completed weeks or more, the woman was counselled regarding ECV if no contra-indications for ECV were present. Women who consented to the procedure were admitted to the ward, and an ultrasound was done to determine the estimated fetal weight, amniotic fluid index, type of breech (flexed/extended), the position of the head (whether hyperextended or not), the position of the placenta and to rule out uterine anomalies. If there were no further contra-indications identified by ultrasound, the procedure was carried out after administration of a tocolytic agent (inj. terbutaline 0.25 mg, subcutaneously). ECV was carried out by the obstetrician, either by the backward flip or forward roll technique. The fetal heart rate was checked before, during and after the procedure using ultrasonography. Following the procedure, bradycardia or non-reassuring fetal heart rate patterns were ruled out, and the woman was observed for rupture of membranes, the onset of labour pains or decreased fetal movements, following which she was discharged from the hospital. After a successful ECV, the patient was followed up regularly in the antenatal clinic, and if she did not go into spontaneous labour, was induced past dates, as per standard of care in our setting. Emergency caesarean delivery was performed for obstetric indications. If, however, the procedure was unsuccessful, in the absence of any contra-indications, the option of vaginal breech delivery was discussed, providing knowledge about benefits and possible complications, to help the patient make an informed decision. If vaginal breech delivery or ECV was contra-indicated, or the woman was unwilling for these procedures, she was planned for an elective caesarean delivery.

Inclusion criteria

All women who presented with a non-cephalic presentation at term and underwent an attempt at ECV were included in the study, and their information was retrieved for analysis.

Statistical analysis

Data was transferred to Microsoft Excel, and statistical analysis was done using SPSS, version 24.0 (IBM Inc., Armonk, NY, USA). Continuous variables were tested for normality using Kolmogorov-Smirnov (K-S) test and Shapiro-Wilk test and continuous variables that were not normally distributed were expressed as median and range and discrete variables as frequencies and proportions. The associations were determined using chi-square test, and a p-value of <0.05 was considered to be statistically significant.

Results

As depicted in Figure 1, a total of 201 women were documented in the register as having undergone an attempt at ECV between October 2012 and June 2020. Of these, one woman had entirely missing data, and six women delivered at other hospitals, hence their delivery records were not available. For the remaining 194 women, baseline demographic information and delivery details were extracted from the hospital electronic database and analysed (Table 1).

Of the women included in the study, 176 of them were within the age group of 20 to 35 years (90.7%), median (range) age

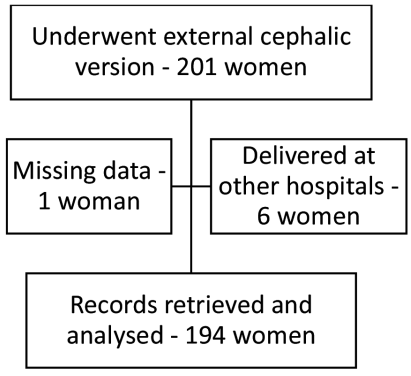


Figure 1. Participants flow diagram

being 24.08 (20) years. Vaginal deliveries comprised 56.7% (110 women) of the total number of deliveries, of which five were vaginal breech deliveries. There were 84 women (43.2%) who underwent caesarean section for various indications including the elective cases who had an unsuccessful ECV. Among the babies delivered in the study group, 77.3% (150 babies) had normal birthweights of 2,500 to 3,500 gm, 9.3% (18 babies) were large for gestational age and 12.9% (25 babies) were low birth weight. One baby (0.5%) was in the very low birth weight category (<1,500 gm). There were 81 male babies and 113 female babies (41.8% and 58.2%, respectively) and 98.9% of the babies were healthy, i.e. normal APGAR score, at the time of delivery (192 out of 194 neonates).

The procedure was observed to be successful in 64% of patients (128 out of 200 women). The denominator for the success rate of ECV calculation was taken as 200 women since the data for immediate outcome of the procedure (i.e. successful/unsuccessful ECV) was available for them. The 6 women who delivered at other hospitals were excluded from the analysis for associations or delivery outcomes. From the available data, associations were studied between maternal age, parity, gestational age at delivery and birth weight of the baby to study factors that could affect the success of ECV. The findings are presented in Table 2.

Table 1. Baseline characteristics

Characteristics		Frequency	%
Age	<20	17	8.8
	20-35	176	90.7
	>35	1	0.5
Parity	Primi	114	58.8
	Multi	80	41.2
Gestational age at ECV*	Preterm	4	2.1
	Term	173	89.2
	Post dates	11	5.7
	Missing	6	-
Mode of delivery	Normal	81	41.8
	Instrumental	24	14.6
	Breech	5	2.6
	Caesarean	84	43.3
Birth weight	VLBW*	1	0.5
	LBW*	25	12.9
	Normal	150	77.3
	LGA*	18	9.3
Sex of baby	Male	81	41.8
	Female	113	58.2
Fetal outcome	Healthy	192	98.9
	Sick	1	0.5
	Stillborn	1	0.5

Maternal age: Median 24.08, range: 20 years
*ECV: External cephalic version, VLBW: Very low birth weight, LBW: Low birth weight, LGA: Large for gestational age

Among the analysed data of women who had successful ECV (n=123), 99 of them (80.4%) delivered vaginally and 24 underwent caesarean section (19.5%). The indications for caesarean section (Figure 2) were: non-reassuring fetal status (n=10), failure to progress (n=4) or failed induction of labour (n=3) and malpresentation (n=3 transverse lie; n=3 breech in labour; and n=1 persistent mentoposterior).

In those for whom ECV was unsuccessful, 11 women (15.4%) delivered vaginally including four vaginal breech deliveries, three suction cup deliveries and four normal vaginal deliveries following spontaneous version. The remaining 60 women (84.5%) were delivered by caesarean section.

For the neonatal outcomes, over 95% of the babies had a normal APGAR at the time of delivery, regardless of success or failure of the procedure, including 122 babies (99.2%) among the successful ECV group and 70 babies (98.5%) among the unsuccessful ECV group. One baby had a 5-minute APGAR score <7, born to a mother in the unsuccessful ECV group, who presented later with a cephalic presentation in labour and had non-reassuring fetal status in second stage, delivered normally with episiotomy. The baby was referred to the tertiary care hospital for therapeutic cooling in view of hypoxic ischemic encephalopathy and is now doing well with normal developmental milestones and being followed up in the

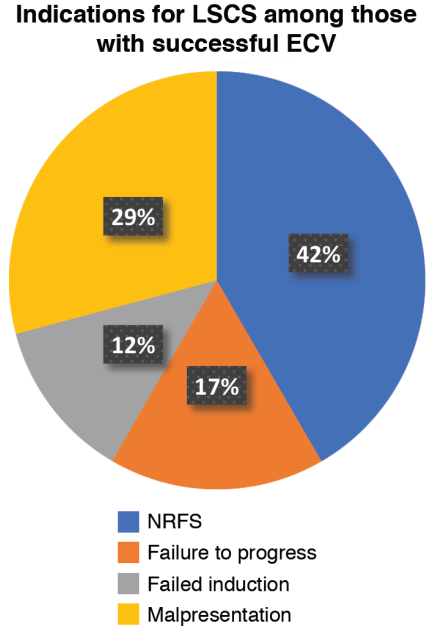


Figure 2. Indications for caesarean section among women who had successful external cephalic version (n=24)
ECV: External cephalic version, LSCS: Lower segment caesarean section, NRFS: Non-reassuring fetal status

outpatient department. There was one intrapartum stillbirth in the successful ECV group, in a woman who was diagnosed to have breech presentation at admission for induction of labour. She underwent ECV with no peri-procedural complications, followed by pre-induction cervical ripening with prostaglandin E1 as per standard of care. She complained of decreased fetal movements the next day and was found on ultrasound to have intra-uterine fetal demise. The baby was born through meconium stained amniotic fluid and there was no other evident cause for the stillbirth identified following delivery including no evident growth restriction or external anomalies.

Only three women had significant procedure related complications. One had persistent severe variable decelerations on non-stress test, warranting an immediate caesarean section, one had pre-labour rupture of membranes, and one woman had a placental abruption. This latter patient had a successful ECV, reactive post-procedure non-stress test and was discharged from hospital to review in the OPD. In addition, she was instructed to report to the labour room in case of any complications, which were explained to her in detail. She presented to the labour ward eight hours later with antepartum haemorrhage, and a diagnosis of placental abruption with non-reassuring fetal status was made, for which she underwent an emergency caesarean section. In all three cases, there were no adverse neonatal outcomes, and the babies all had normal APGAR at delivery and an uneventful neonatal period.

Discussion

This retrospective review was undertaken with the aim of determining the success rate of ECV for women presenting with a non-cephalic presentation at term. A further aim was to study both maternal and fetal delivery outcomes of these women, and to see if there were any significant peri-procedural complications.

The success rate of ECV was found to be 64%, which is comparable to the success rate of approximately 60-65% from other reported international and national data (8,10). From a previous meta-analysis done in 2008, it was established that certain factors, such as multiparity, gestational age, non-engagement of the presenting part and administration of a tocolytic were specific clinical factors that predicted successful ECV (11). In our study group, all patients were administered a tocolytic and there was no documentation of engagement/non-engagement of the presenting part in our records. Multiparous women were found to be more likely to have a successful procedure (75% multiparous vs 55.3% primiparous) and this difference was statistically significant. Although the recommendation is to perform ECV by 36 completed weeks in primigravidae and 37 completed weeks in multigravidae, the gestational age at the time of ECV was not found to be significantly associated with success or failure of the procedure (Table 2).

A successful ECV also had a positive impact on the mode of delivery with a majority of these women delivering vaginally, with a cephalic presentation (80.5%) compared to those who had an unsuccessful ECV, with only 15.5% vaginal deliveries. This outcome was statistically significant with $p<0.001$ and an odds ratio of 22.5. It should also be noted that among those who had an unsuccessful ECV, seven out of 11 women eventually presented as cephalic and delivered vaginally. This emphasises the possibility of spontaneous version, even after a failed ECV attempt, and the importance of rechecking and making a correct diagnosis of presentation, even if the woman is admitted for a planned caesarean following "failed ECV".

Table 2. Factors affecting the success of external cephalic version

Factors		ECV		OR (95% CI)	p
		Success (n, %)	Failure (n, %)		
Age (years)	<30	113 (62.8)	67 (37.2)	0.675 (0.204-2,236)	0.580 (Fischer's)
	≥30	10 (71.4)	4 (28.6)		
Parity	Primi	63 (55.3)	51 (44.7)	2,429 (1,298-4,544)	0.005
	Multi	60 (75)	20 (25)		
Gestational age at ECV*	Appropriate[1]	86 (60.6)	56 (39.4)	0.605 (0.293-1,249)	0.172
	Not appropriate[2]	33 (71.7)	13 (28.3)		
Birth weight (kg)	<3.5	109 (62.6)	65 (37.4)	0.719 (0.263-1,962)	0.518
	>/= 3.5	14 (70.0)	6 (30.0)		

[1]Appropriate gestational age is defined as before 36 completed weeks for primis and 37 completed weeks for multis, [2]Not appropriate gestational age is defined as beyond 36 completed weeks for primis and 37 completed weeks for multis, *For the other variables n=194 (women with delivery details available); for gestational age at ECV n=188 since 6 women had missing data regarding gestational age in the ECV register.
ECV: External cephalic version, OR: Odds ratio, CI: Confidence interval

The women who had a successful ECV were significantly more likely to deliver vaginally compared with those who had an unsuccessful ECV (p<0.001). Only 19.5% of women who had a successful ECV needed a caesarean section for delivery (Table 3). This is comparable to the findings of another study from Hong Kong, which found 19.7% women who underwent caesarean deliveries following successful ECV (12). The caesarean deliveries in the ECV success group with a vertex presentation was only 13.8% compared to the 24% rate reported by Stine et al. (13).

Among the neonatal outcomes, there was a slightly higher proportion of perinatal morbidity (5-minute APGAR score <7)/mortality, following unsuccessful ECV compared with successful ECV (1.4% vs 0.8%, respectively) but this difference was not significant (Table 4). A similar study done in a rural tertiary care hospital in Maharashtra reported all babies to have APGAR of 9 at 5 minutes and no fetal complications or deaths attributable to ECV (14). No difference in perinatal outcome has been seen in other higher-powered studies either, rather showing comparable outcomes in both groups (15). The overall low peri-procedural complication rate observed (1.5%) is consistent with findings across other studies (15-17). We observed one minor (prelabour rupture of membranes) and two major (one placental abruption and another fetal distress requiring immediate caesarean delivery) procedure related complications, as discussed earlier.

Study limitation

The chief limitation of this study is the retrospective design, due to which much data, as well as additional parameters that could have affected the outcome, were not retrieved. We were not able to study the association between success of the procedure and other factors such as estimated fetal weight and other ultrasound features including type of breech, amniotic fluid index at the time of ECV and maternal body mass index, due to incomplete data. At the beginning of the study period, the out-patient charts and discharge summaries for all in-patients were manually hand-written records which were archived in the medical records department, making them difficult to retrieve for additional relevant information. During the latter part of the study, the medical information entry format became digital with scanned out-patient charts and online discharge summaries. Due to this change in the data entry format, there was a lack of uniformity in data availability.

Conclusion

The results of this study suggest that ECV is a useful procedure in women with breech presentation at and near term, with no contra-indications for a vaginal delivery. Converting the fetal presentation to cephalic gives the opportunity for a normal vaginal delivery, thereby reducing the neonatal morbidity of a vaginal breech delivery and the maternal morbidity of a caesarean section. If the option of ECV for breech presentation was not considered, the majority of those women would have undergone a primary caesarean section. Therefore, this procedure has a definite role in reducing the number of primary caesarean sections and also has a low overall complication rate, making it a useful tool for obstetric management, especially in limited resource settings.

Table 3. Association between external cephalic version success and mode of delivery

Factors		Mode of delivery		OR (95%CI)	p
		Vaginal	Caesarean		
ECV	Success (n, %)	99 (80.5)	24 (19.5)	22.5 (10.29-49.20)	<0.001
	Failure (n, %)	11 (15.5)	60 (84.5)		
ECV: External cephalic version, OR: Odds ratio, CI: Confidence interval					

Table 4. Association between external cephalic version success and neonatal outcome

Factors		Foetal outcome		OR (95% CI)	p (Fischer's exact)
		Healthy	Sick		
ECV	Success (n, %)	122 (99.2)	1 (0.8)	1,743 (0.107-28,300)	1,000
	Failure (n, %)	70 (98.5)	1 (1.4)		
ECV: External cephalic version, OR: Odds ratio, CI: Confidence interval					

Ethics Committee Approval: *Obtained from the Institutional Review Board and Ethics Committee CMC Vellore, (IRB number: 11412).*

Informed Consent: *It couldn't be obtained in view of the retrospective nature of the study.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Surgical and Medical Practices: A.G.C., T.A.M.; Concept: A.G.C., T.A.M.; Design: T.A.M., A.G.C.; Data Collection or Processing: A.G.C., T.A.M.; Analysis or Interpretation: S.J., S.M.D., T.A.M., D.J.; Literature Search: T.A.M.; Writing: T.A.M., A.G.C., S.J.*

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

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

References

1. Hickok DE, Gordon DC, Milberg JA, Williams MA, Daling JR. The frequency of breech presentation by gestational age at birth: a large population-based study. Am J Obstet Gynecol 1992; 166: 851-2.
2. Hannah ME, Hannah WJ, Hewson SA, Hodnett ED, Saigal S, Willan AR. Planned caesarean section versus planned vaginal birth for breech presentation at term: a randomised multicentre trial. Term Breech Trial Collaborative Group. Lancet 2000; 356: 1375-83.
3. Stafford RS. Recent trends in cesarean section use in California. West J Med 1990; 153: 511-4.
4. Hofmeyr GJ, Hannah M, Lawrie TA. Planned caesarean section for term breech delivery. Cochrane Database Syst Rev 2015; CD000166.
5. Cooper GM, Lewis G, Neilson J. Editorial I: Confidential enquiries into maternal deaths. Br. J. Anaesth 2002; 89: 369-72.
6. Hall MH, Bewley S. Maternal mortality and mode of delivery. Lancet 1999; 354: 776.
7. Walker R, Turnbull D, Wilkinson C. Strategies to address global cesarean section rates: a review of the evidence. Birth 2002; 29: 28-39.
8. Zhang J, Bowes BA Jr, Fortney JA. Efficacy of external cephalic version: a review. Obstet Gynecol 1993; 82: 306-12.
9. External Cephalic Version. Practice Bulletin No 161. American College of Obstetricians and Gynaecologists. Obstet Gynaecol 2016;127:e54-61.
10. Kathpalia S, Singh Y, Sharma R. Outcome of external cephalic version for breech presentation. Med J Armed Forces India 2012; 68: 151-3.
11. Kok M, Cnossen J, Gravendeel L, van der Post J, Opmeer B, Mol BW. Clinical factors to predict the outcome of external cephalic version: a metaanalysis. Am J Obstet Gynecol 2008; 199: e1-7.
12. Lau TK, Lo KW, Michael Rogers M. Pregnancy outcome after successful external cephalic version for breech presentation at term; Am J Obstet Gynecol 1997; 176: 218-23.
13. Stine LE, Phelan JP, Wallace R, Eglinton GS, van Dorsten JP, Schifrin BS. Update on external cephalic version performed at term. Obstet Gynecol 1985; 65; 642-6.
14. Vedpathak SG, Korde Nayak VR, Panigrahi PP. Outcome of external cephalic version (ECV) in singleton pregnancy with uncomplicated breech presentation at term in a tertiary rural hospital. Int J Reprod Contracept Obstet Gynecol 2017; 6: 3528-32.
15. Nassar N, Roberts CL, Barratt A, Bell JC, Olive EC, Peat B. Systematic review of adverse outcomes of adverse external cephalic version and persisting breech presentation at term. Paediatr Perinat Epidemiol 2006; 20: 163-71.
16. Beuckens A, Rijnders M, Verburgt-Doeleman GH, Rijninks-van Driel GC, Thorpe J, Hutton EK. An observational study of the success and complications of 2546 external cephalic versions in low-risk pregnant women performed by trained midwives. BJOG 2016; 123: 415-23.
17. Rodgers R, Beik N, Nassar N, Brito I, de Vries B. Complications of external cephalic version: a retrospective analysis of 1121 patients at a tertiary hospital in Sydney. BJOG 2017; 124: 767-72.

The immunohistochemical and histologic effects of contrast medium on uterus, fallopian tubes and ovaries, given during hysterosalpingography: rat study

Eren Pek[1], Ceren Canbey Göret[2], Servet Hacıvelioğlu[3], Gürhan Adam[4], Mesut Abdülkerim Ünsal[3]

[1]Clinic Obstetrics and Gynecology, Dinar State Hospital, Afyonkarahisar, Turkey

[2]Clinic of Surgical Pathology, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital, İstanbul, Turkey

[3]Department Obstetrics and Gynecology, Çanakkale Onsekiz Mart University Health Practice and Research Hospital, Çanakkale, Turkey

[4]Clinic of Radiology, Memorial Şişli Hospital, İstanbul, Turkey

Abstract

Objective: Previous studies have shown that damage occurs to internal genital tract during hysterosalpingography (HSG). The aim was to show that endometrial and tubal epithelium underwent free radical damage during HSG in an animal model.

Material and Methods: Forty rats were evaluated in five different groups. Two groups received ionizing radiation (15-20 miliRad three times) only. Two further groups received ionizing radiation in combination with iohexol (1-2 mL). The remaining group served as control. Groups were evaluated after seven and forty-two days. Inflammation and cellular changes were evaluated histopathologically. Cellular activity of antioxidant enzymes was assessed immunohistochemically.

Results: Inflammation, and cellular changes were detected at certain rates in all groups ($p<0.001$). Glutathione reductase, catalase, superoxide dismutase, glutathione S-transferase activities were found to be increased after the HSG ($p<0.001$).

Conclusion: It is obvious that the cell suffers acute and chronic damage during HSG due to both radioactivity and chemicals. Although there is a lot of research done before, there is no definitive method yet to protect against the harmful effects of iodinated contrast agents and ionizing radiation. So, new methods need to be explored to protect cells and tissues from reactive oxygen radical damage caused by HSG. (J Turk Ger Gynecol Assoc 2020; 21: 243-54)

Keywords: Free oxygen radicals, hysterosalpingography, iohexol, ionizing radiation

Received: 07 April, 2019 **Accepted:** 15 May, 2020

Introduction

Infertility is a condition that prevents the conception of children. The diagnosis of infertility is usually given to couples who have been attempting to conceive for at least one year without success (1,2). It is estimated to affect between 8% and 12% of reproductive-age couples worldwide. In female infertility, approximately 30% to 40% of cases involve ovulatory dysfunction, and 30% to 40% involve tubal and pelvic pathology; 30% of cases are attributed to other unexplained causes, of which reproductive age may be an important contributor (3). Therefore, evaluation of tubal patency and the uterine cavity is important for treatment. Hysterosalpingography (HSG) is one of the oldest imaging techniques. It uses standard X-ray procedures with ionizing radiation and has been used for tubal patency testing for a long time.

It should be noted that this technique has limited accuracy with a positive predictive value 38%. Thus it has been replaced by specific ultrasound procedures, especially with air/saline, foam, and Doppler (4). However, in many places, the original

Address for Correspondence: *Eren Pek*
e.mail: drerenpek@hotmail.com ORCID: orcid.org/0000-0003-1060-9613

Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2020.2019.0067

procedure is still a basic method and recommended as the first-line diagnostic tool because it does not require highly qualified practitioners (5-7). However, there is clear evidence that the rapidly dividing cells of the reproductive system will be damaged during HSG (8,9). There has been a great deal of research into minimizing the cellular damage to reproductive cells caused by HSG, as well as studies into reducing the negative effects of ionizing radiation and iodinated contrast media on other organ systems (10-13). However, there is no totally effective method of protection currently available so that minimum doses of ionizing radiation and the use of contrast, only when absolutely necessary, are the mainstays of reducing the deleterious effects of imaging studies. Previous studies investigating the early and late cellular effects of iohexol, an iodinated contrast agent, and ionizing radiation on the uterus, tubes and ovaries have been inconclusive. Given that HSG is a diagnostic method used in women who already have low reproductive capacity further clarification of these effects is important. The aim of this study was to investigate the effects of HSG, with and without iodinated contrast, on endometrium, tubes and ovarian epithelial cells in an animal model.

Material and Methods

This study was performed in the Laboratory Center for Experimental Studies of Çanakkale Onsekiz Mart University with the approval of the University's Laboratory Animals Ethics Committee (approval number: 2016/01-02).

Animals: Forty female Wistar albino rats, aged 12-14 weeks, with regular cycles and weighing 250-300 g were kept under a 12-hour artificial light/dark cycle at a temperature of 20-24 °C. The animals were kept in groups of five per cage, and were fed with standard pellets and tap water. All rats in the estrous cycle (estrus phases of rats were confirmed by vaginal cytology) were randomly divided into five (n=8) experimental groups designated A, B, C, D and E. The number of rats in each group was set as the minimum number that could be statistically significant to prevent animal wastage.

Chemicals: Clinical substances were obtained from GeneTex glutathione S-transferase pi 1 antibody GSTP1 GTX31766-100 (GeneTex, Inc. CA/USA), GeneTex glutathione reductase antibody N2C2 GTX114199-100 (GeneTex, Inc. CA/USA), Novusbio superoxide dismutase antibody SOD1 NBP224915 (Novus Biologicals, LLC. CO/USA) and Novusbio catalase antibody CAT NBP2-24916 (Novus Biologicals, LLC. CO/USA). DAKO (Agilent: Chemical Analysis, Life Sciences, and Diagnostics, Santa Clara, CA/USA) automatic dyeing machine was used for immunohistochemical staining. Iohexol (Omnipaque 350 mg/100 mL, Opakim Medical Products Industry and Trade Corporation. İstanbul /Turkey) was used as radiocontrast medium.

Experimental design: The procedural steps were performed as detailed in Table 1.

Surgical, radiation and iohexol application procedure: 400 mg/kg/intraperitoneal dose of chloral hydrate was administered

Table 1. Details of experimental procedures applied to each group of animals

Group	n/n	Time (in days)	Procedure
A	8/8	0	Control group. No additional procedure was implemented (see below). The uterus, fallopian tubes, and ovaries were removed under the anesthesia.
B	8/7	0-7	After laparotomy, rat abdomens were closed without any intervention under the anesthesia. Then, 15-20 mRad/dose radiation was administered three times (in the 1st, 3rd, and 15th minute). Seven days later laparotomy was performed again, and the uterus, tubes, and ovaries of rats were removed under the anesthesia.
C	8/6	0-7	After the laparotomy under the anesthesia, iohexol (10 mL/kg) was administered by a canule through the cervix. The procedure was terminated after the tubes were filled, and when contrast matter was observed in the abdomen. Then, the abdomens were closed and animals exposed to X-ray (at the same dose and time), similar to other rats. Seven days later laparotomy was performed again, and the uterus, tubes, and ovaries of rats were removed under anesthesia.
D	8/7	0-42	After laparotomy, rat abdomens were closed without any intervention under the anesthesia. Then, 15-20 mRad/dose radiation was administered three times (in the 1st, 3rd, and 15th minute) to the rats. 42 days later laparotomy was performed again, and the uterus, tubes, and ovaries of rats were removed under the anesthesia.
E	8/7	0-42	After the laparotomy under the anesthesia, iohexol (10 mL/kg) was administered by a canule through the cervix. The procedure was terminated after the tubes were filled, and when contrast matter was observed in the abdomen. Then, the abdomens were closed and animals exposed to X-ray (at the same dose and time), similar to other rats. Forty-two days later laparotomy was performed again, and the uterus, tubes, and ovaries of rats were removed under the anesthesia.

for anesthesia (8). On the first day, after skin cleaning the rats with 10% batticon, a midline incision (approximately 2 cm) was made to access the abdominal cavity. This incision process was applicable to all groups. Then eight rats were directly sacrificed, and the uterus, tubes, and ovaries were removed (group A). In groups C and E, subsequent to incision, 1-2 mL of iohexol was introduced via an injector to the animals' cervix (Figure 1A). Next, the other groups, with the exception of group A, were exposed to radiation (Figure 1B, C). In groups B and D all-body irradiation was applied at a dose of 15-20 miliRad three times with 3-minute intervals to the rats after opening of the abdomen. Groups C and E also received three doses of total body irradiation; the first dose radiation was given while iohexol was injected and then the other two doses were given in the same way as for groups B and D.

The abdomens of the rats in all groups were closed continuously using absorbable suture materials (4.0 vicryl-rapide) after surgical procedures were completed. For the evaluation of acute (early) effects, after seven days laparotomy was performed again in groups B and C. In groups D and E repeat laparotomy was performed after forty-two days for the evaluation of chronic (late) effects and the uterus, tubes and ovaries were removed.

Preparation for pathological and immunohistochemical evaluation: The pathological materials were preserved in 10% formaldehyde and fixed. Two different histological preparations were undertaken. Sections with a thickness of 3-5 microns were prepared from all tissues removed. One group of tissue sections were stained with hematoxylin and eosin for histopathological evaluation under the light microscope. The other group of tissues were embedded in paraffin and 4-5 micron-thick sections were taken for immunohistochemical examination. Sections were stained with antibodies specific for glutathione S-transferase, glutathione reductase, superoxide dismutase and catalase.

Histopathological scoring: Vascular ectasia, inflammation, and epithelial cytological and architectural features were evaluated and scored using objective criteria by the same pathologist (8,14,15). Epithelial architectural features; (a) tufting, (b) stratification, (c) chromatin disorganization, (d) irregularity in nucleus contour, (e) increases in nucleus size and ratio of nucleus/cytoplasm, (f) pleomorphism, (g) presence of nucleoli, (h) mitosis and (i) hyperchromasia. All the criteria evaluated except inflammation and vascular ectasia were reported as cellular changes. A minimum of five fields were evaluated on each tissue slide with 40 and 400 magnification and assigned scores for severity of changes as follows: no effect or no staining (0), mild effect or poor staining in localized areas (1), the presence of moderate influence or moderate staining (2) and severe effect or strong staining (3). The other sections which were prepared for immunohistopathological assessment (glutathione S-transferase, glutathione reductase, superoxide dismutase, and catalase) were again evaluated by the same pathologist and the same scoring system was used.

Statistical analysis

For statistical analysis, SPSS version 20.0 was used (IBM Inc., Armonk, NY, USA). Descriptive statistics was used to calculate the mean scores and standard deviations of each evaluated histopathological finding. (mean ± standard deviation). Statistically, the Kruskal-Wallis H-test was used to determine whether mean differences were significant in terms of group variables, and Mann-Whitney U test was used to determine the group from which the differences originated. Significance was accepted at $p<0.05$.

Iohexol, ionizing radiation and measured antioxidant enzymes

Understanding the mechanism of damage caused by ionizing radiation and iodinated contrast media to cells and tissues will be useful here. Iohexsol is a water-soluble, non-ionic, monomeric and low-osmolarity iodinated contrast media. It may show direct cellular toxicity or it may cause indirect toxic effects through the formation of reactive oxygen radicals. This effect is mediated by the release of vasoconstrictor substances such as adenosine, endothelin, vasopressin, angiotensin 2 and dopamine. The result is hypoxia and the release of free oxygen radicals (16,17). Osmolarity is thought to be an especially important factor in these effects. However, osmolarity alone is insufficient to explain this situation. The osmolarity of mannitol is similar to some iodinated contrast agents, but the pathological effects are not the same (18). Thus it is useful to ask whether the use of antioxidants and vasodilating agents are protective against this effect? Many studies have investigated this question. Melatonin, L-carnitine, vitamin C, vitamin E, amifostine, amlodipine, curcumin, N-acetylcysteine and trichloroacetic acid have all been studied (8-11,15,19-24). The effects of radiation on living tissues can be divided into four stages. In the first step, energy is transferred to the substance. This stage is known as the physical step and causes ionization of the substance. The products that appear after the first stage are unstable and cause reactive products. This second stage is the physico-chemical stage. In the chemical stage, the third stage, reactive products interact with cellular structures. The result is production of free radicals. The biological step is the final stage and starts with enzyme reactions that cause a variety of damage, including DNA molecular damage. However, some of this damage can be repaired. Damage that cannot be repaired leads to cell death (25). Physico-chemical changes caused by ionizing radiation in the cell are very rapid (less than

a second). In contrast, it may take hours, days, months or even years for biological results to occur. Ionizing radiation causes the breaking of chemical bonds in intracellular molecules, especially chromosomes. If this genetic damage, including de novo mutations, are not corrected by repair mechanisms, they can lead to apoptosis. However, if there is no cell death, they may result in cancer at some point in the future. The effects from energy absorption are direct effects. On the other hand, there are indirect effects that occur through the formation of free oxygen radicals (26,27). Water molecules maybe ionized when the cell is exposed to radiation. A positively charged water molecule and free electrons are formed. Free electrons combine with another water molecule to form a negatively charged water molecule. Positive and negative water molecules are unstable and break down to form ions and free radicals (28-30). Cells with higher reporoductive turnover, such as those found in the genital system and reproductive cells, are more sensitive to radiation. Cells are most susceptible to cell death during the G2 stage and mitosis (31,32). The first response to oxidative stress from the cell is through antioxidant enzymes. The most important enzymes in this response are glutathione peroxidase, superoxide dismutase, catalase and glutathione reductase. Other non-enzymatic defenses include antioxidant compounds such as vitamin E, vitamin C, beta carotene, transferrin, ceruloplasmin, haptoglobin and albumin (33,34). The most important enzymic activity is catalyzed by superoxide dismutase which breaks down superoxides. When superoxides are broken down, hydrogen peroxide is formed (35) and catalase will inactivate hydrogen peroxide (36). During these events, glutathione S-transferases act as catalysts (37,38). Glutathione reductase is an enzyme that converts oxidized glutathione, which occurs during reactions catalyzed by glutathione S-transferase, to reduced glutathione (39). Therefore, the aim in this study was to measure the activity of each of these enzymes in the cell using immunohistochemical staining.

Results

Considerable cellular and histopathological changes were observed for all other groups and criteria when compared to the control group.

First, the normal glandular and columnar epithelium sections of the control group were examined. Figure 1D shows a normal section from the control group. The entire assessment was carried out by the same pathologist. The status of the basal metabolic activity of a normal cell from the control group was evaluated immunohistochemically and histopathologically. This was used as a baseline for comparison and was assigned a score of "0" score, corresponding to the "no effect or no staining" condition.

Inflammation: Inflammation was detected intensely in all groups and a statistically significant difference was found between scores for the experimental groups compared to

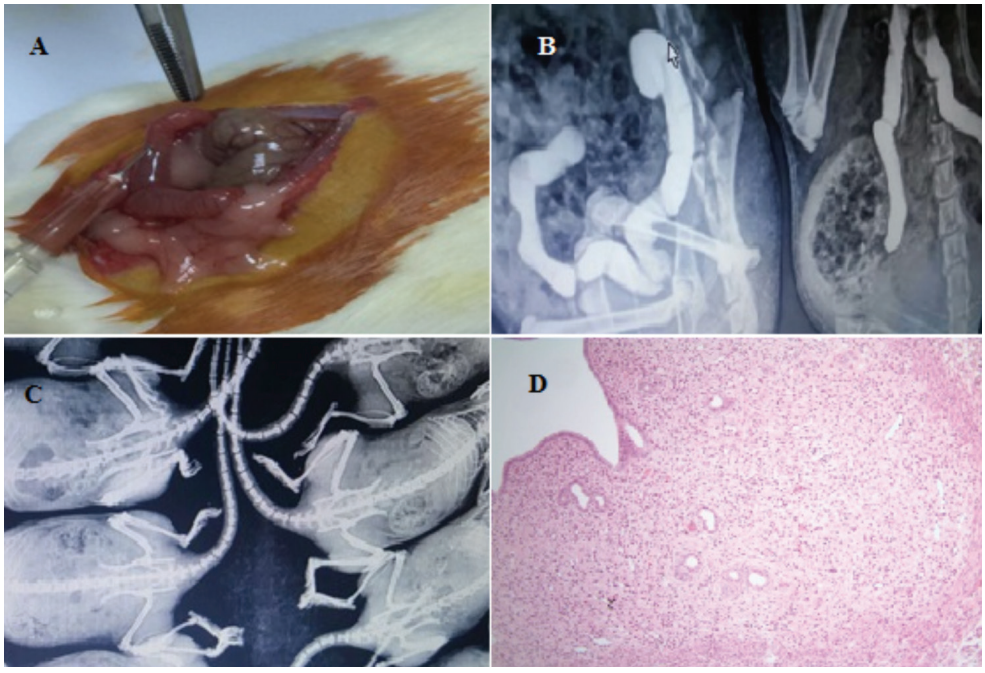


Figure 1. (A) Uterine injection of radiocontrast material from the rat's cervix with a tuberculin injector. (B) The hysterosalpingography image after the iohexol injection. (C) The hysterosalpingography image which the group without radiocontrast agent. (D) The normal appearance of endometrium and columnar epithelium and glandular epithelium (hematoxylin-eosin staining, x40) (the image of histological section of group A)

the control group (p<0.001). Ionizing radiation-induced inflammation was more evident in the acute phase (group B) than in chronic phase (group D). As a result of the histopathological evaluation of inflammatory changes using numerical scoring system, it was determined that group C received the highest scores arithmetically. Thus, inflammation scored higher in the early stage of conditions where the cell was exposed to ionizing radiation with together iohexol (Figure 2A, B and 3A, B).

Cellular changes: When compared to the control group, major changes were observed in the structure of cells in all groups (p<0.001). The most severe changes were seen in the chronically exposed animals' tissues. When each group was evaluated separately it was striking that iohexol increased the deleterious effects of ionizing radiation (Figure 2A, B).

Vascular ectasia: The results were statistically significant in all other groups compared to the control group (group A) (p=0.009). Vascular ectasia was more evident in group C. (Figure 3A, B).

Immunohistochemical evaluation results: The activity of all antioxidant enzymes were increased in animals exposed to both iohexol and ionizing radiation. In addition the effects were more marked in chronic exposure animals compared to acutely exposed animals.

- **Glutathione Reductase:** Glutathione reductase activity was observed to be increased at different rates in all groups compared to the control group as a result of immunohistochemical examination (p<0.001) (Figure 4A, B).
- **Catalase:** For catalase activity, we found significant histological differences in all groups to compared with the control group (p<0.001) (Figure 5A).
- **Superoxide dismutase:** Superoxide dismutase activity was more intense in all study groups rather than control group (p<0.001) (Figure 5B).
- **Glutathione S-transferase:** When all groups were compared with the control group, we detected increased changes at different intensities (p<0.001) (Figure 6A, B).

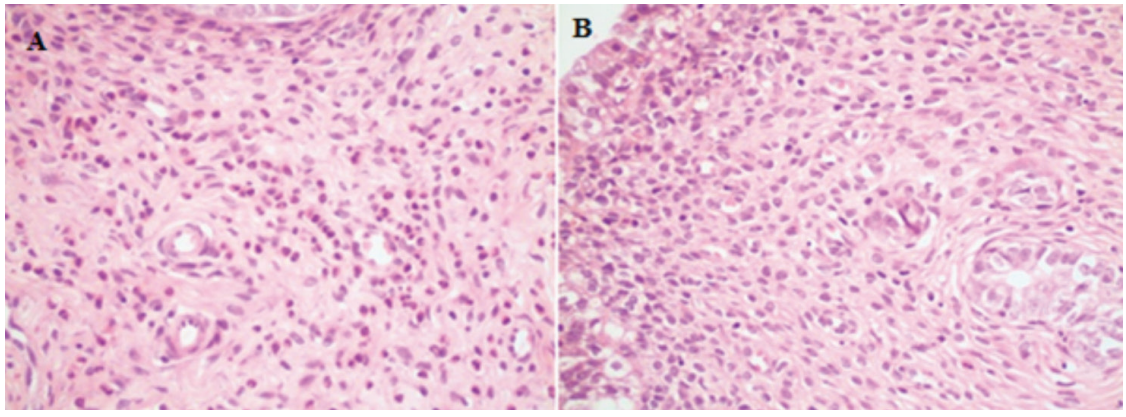


Figure 2. (A) Mix type intense inflammation in endometrial stroma; mainly consisting of the eosinophilic leukocytes (group B) (hematoxylin-eosin staining, x400) (B) mild reactive changes and mild inflammation in superficial cells (group E) (hematoxylin-eosin staining, x400)

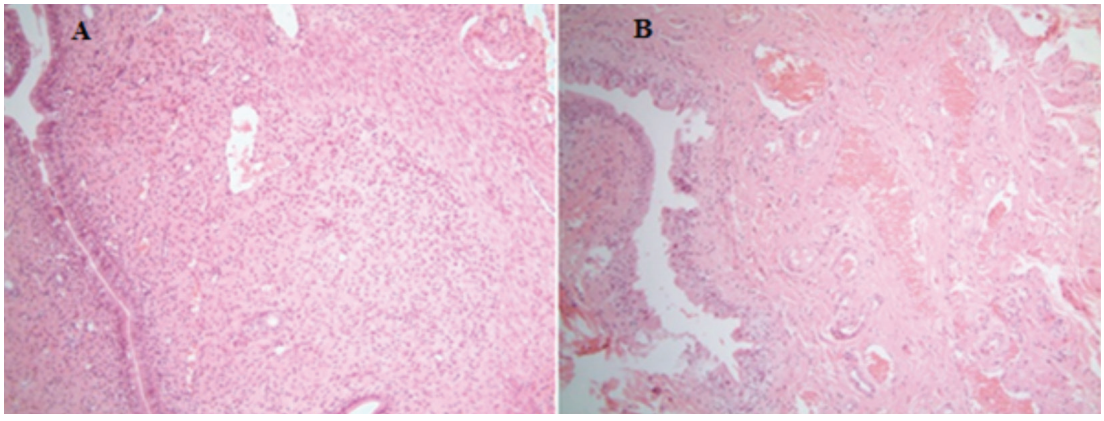


Figure 3. (A) Reactive changes in superficial cells, mix type of mild inflammation in the stromal areas and moderate vascular ectasia (group D). (Hematoxylin-eosin staining, x400) (B) intensive vascular congestion, mix type of mild stromal inflammation, reactive changes in superficial cells (group C). (Hematoxylin-eosin staining, x40)

Interpretation of results (Table 2): Group E exhibited the lowest levels of inflammation compared to the other experimental groups, apart from control animals. This should be no surprise as the first response of the cell to trauma is inflammation among the parameters which we evaluated. At the end of the inflammatory process, the cell will either rescue itself, or undergo apoptosis or a necrotic uncontrolled process. Groups E and D contained the chronically exposed animals. Therefore, the expected result is a greater degree of inflamation in the acute groups - groups C and B. This finding was confirmed in our study.

Vascular ectasia was more dense in the acute period, in a similar fashion to greater inflammation. This may be due to vascular ectasia and congestion being a part of the inflammatory process.

As can be seen from Table 2, anti-free oxygen radicals enzyme activity is more intense in the late (chronic) period. The presence of iohexol is an additive factor to the formation of

Table 2. Comparison of parameters by groups

Variable	Group	n	Mean ± SD	Kw	p	Effects
Cellular changes	A	8	0.250±0.463	20,163	<0.001	E>C>D>B chronic>acute
	B	7	1,571±0.535			
	C	6	2,167±0.753			
	D	7	2,143±0.690			
	E	7	2,286±0.756			
Vascular ectasia	A	8	0.625±0.518	13,538	0.009	C>D>B>E acute>chronic
	B	7	1,571±0.535			
	C	6	2,000±0.894			
	D	7	1,857±0.690			
	E	7	1,429±0.535			
Inflammation	A	8	0.375±0.518	21,383	<0.001	C>B>D>E acute>chronic
	B	7	1,857±0.690			
	C	6	2,333±0.516			
	D	7	1,714±0.488			
	E	7	1,286±0.488			
Glutathione reductase	A	8	0.750±0.463	21,206	<0.001	E>D>B>C chronic>acute
	B	7	2,143±0.690			
	C	6	2,000±0.633			
	D	7	2,286±0.488			
	E	7	2,714±0.488			
Catalase	A	8	0.625±0.518	23,258	<0.001	E>D>B>C chronic>acute
	B	7	1,857±0.378			
	C	6	1,833±0.753			
	D	7	2,000±0.000			
	E	7	2,571±0.535			
Superoxide dismutase	A	8	0.875±0.354	20,950	<0.001	E=D>C>B chronic>acute
	B	7	1,857±0.690			
	C	6	2,000±0.633			
	D	7	2,571±0.535			
	E	7	2,571±0.535			
Glutathione S-transferase	A	8	0.875±0.354	21,675	<0.001	E>D>C>B chronic>acute
	B	7	1,714±0.488			
	C	6	1,833±0.408			
	D	7	2,000±0.577			
	E	7	2,571±0.535			

SD: Standard deviation

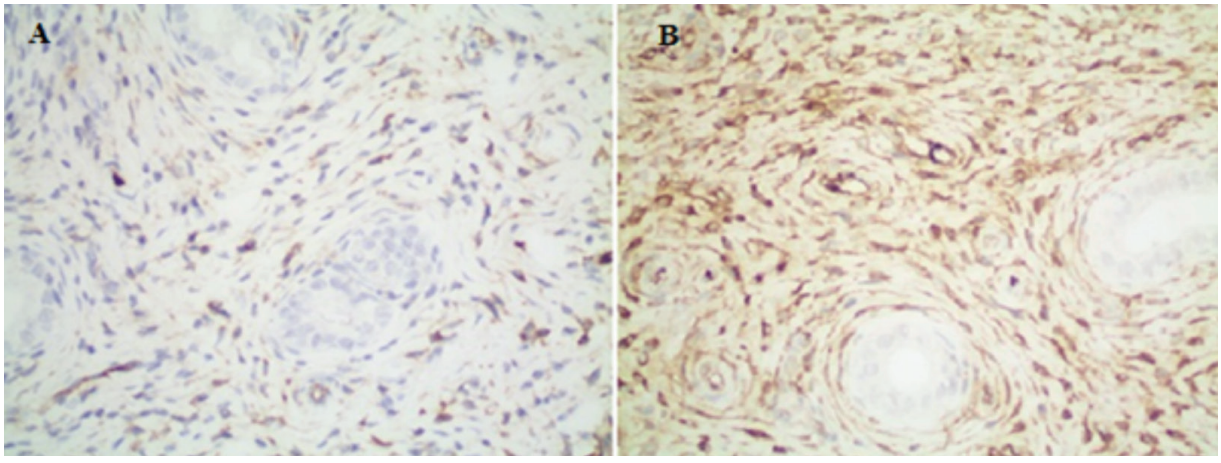


Figure 4. (A) Mild immunohistochemical positivity seen that when the tissue stained with glutathione reductase (group B). (Immunohistochemical glutathione reductase staining, x400) (B) severe immunohistochemical positivity with glutathione reductase (group E) (immunohistochemical glutathione reductase staining, x400)

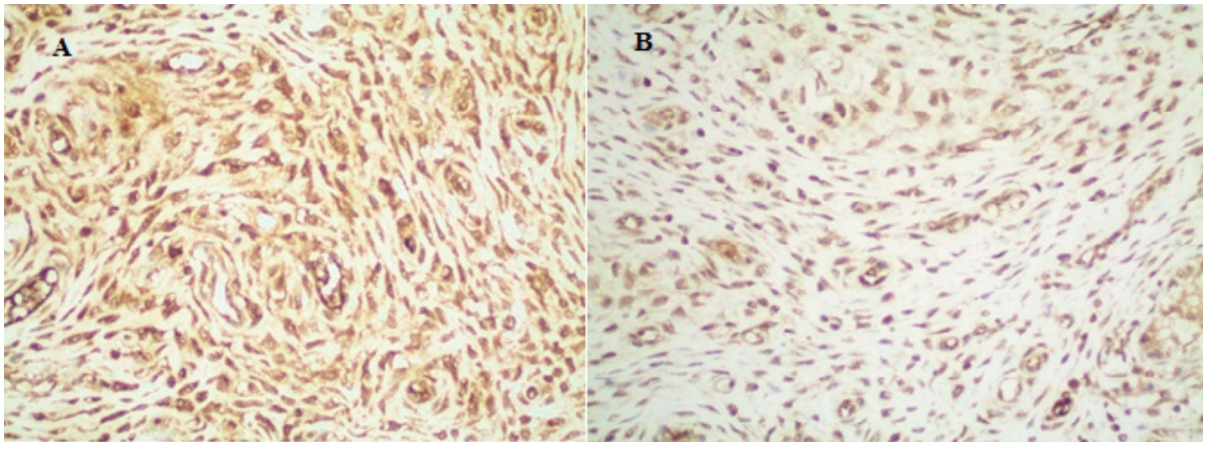


Figure 5. (A) Immunohistochemically severe positivity with Catalase (group E) (immunohistochemical Catalase staining, x400) (B) immunohistochemically severe positivity with superoxide dismutase (group D). (Immunohistochemical superoxide dismutase straining, x400)

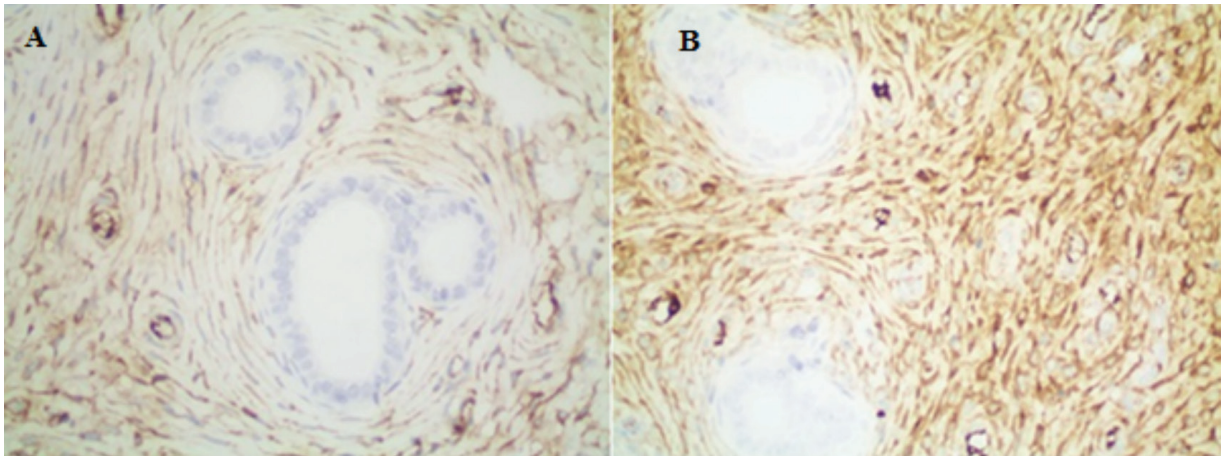


Figure 6. (A) Immunohistochemically moderate positivity with Glutathione S-transferase (group B) (immunohistochemical Glutathione S-transferase staining, x400) (B) immunohistochemically severe positivity with Glutathione S-transferase (group E) (immunohistochemical Glutathione S-transferase staining, x400)

free oxygen radicals caused by ionizing radiation. As a result the greatest cellular damage was found in the chronic groups and was more marked in animals exposed to both iohexol and ionizing radiation compared to those only exposed to the radiation.

Discussion

HSG, which should be done in the follicular phase of the cycle, evaluates the contour of the uterine cavity, cervical canal, and tubal lumina. It is one of the basic tools for infertility diagnosis and has become a standard test for evaluation of infertility worldwide. This procedure is also useful for evaluation of Mullerian system anomalies, recurrent pregnancy losses, abnormal uterine bleeding or amenorrhea and cervical insufficiency. During HSG contrast material is injected into the uterus and this material migrates into the fallopian tubes. Then a series of X-rays, or fluoroscopy is performed. The contrast material shows white in the images allowing any abnormality of structure to be detected. However, the short- and long-term effects of ionizing radiation and contrast medium on tissues are not known. The results of this study show that HSG, a widely used diagnostic technique, may lead to cellular injury and damage to reproductive tissues. Imaging methods using ionizing radiation play an important role in the early diagnosis and treatment of diseases. In diagnosis and treatment, there is the possibility of radiation-induced damage to the patient despite the radiation dose being kept as low as possible and radiation precautions being taken (40). There is no realistic prediction of the diversity and size of health problems that will occur in living organisms at low doses (≤10 cGy) of ionizing radiation. In this respect, low-dose ionizing radiation should not be viewed as safe or tolerable under any circumstances because, due to radiation and independent of the dose, somatic mutations may develop that may lead to neoplastic and non-neoplastic diseases (41). Ionizing radiation may directly and/or indirectly produce various effects in DNA by reactive free radical production (42-44). The effects of ionizing radiation can occur in two different ways; stochastic or deterministic effects. Stochastic effects are independent of the exposure dose. It may even occur at very low doses (40). These types of damage are important subsequent to HSG. In addition, the presence of other factors, such as the total radiation dose received, cellular defence mechanisms, the dose given in each session, the duration of exposure, simultaneous chemicals, and other factors that may lead to proto-oncogen activation, increases ionizing radiation-related damage. When cells are exposed to ionizing radiation during mitosis and the G0-G1 phases, the frequency of unstable dicentric chromosomes increases and chromosome aberrations may occur, due to incorrect regulation of chromosomal fragments (40,45-47). In this respect, even low-dose ionizing radiation should not be viewed as safe or tolerable under any circumstances. Any exposure to ionizing radiation, independent of dose may eventually result in neoplastic change or non-neoplastic disease. DNA alterations and breaking to double-strand occur in cells exposed to ionizing radiation. Activation of phosphorylase and kinases prevent DNA repair, and consequently the G1, S, and G2 cell cycles cannot proceed, leading to cellular death through various mechnisms including apoptosis, mitotic catastrophy, and terminal binding (48). HSG is done in the proliferative phase of the cycle, in order to sure that the woman is not pregnant when the procedure is performed. So, basal cells which will start mitosis, will be more affected by radiation, during this process. Analysis methods at the cell and tissue level are very important to explain possible early and late effects of radiation on different tissues. The total radiation exposure to the patient during HSG withdrawal was calculated as 713 cGy/cm^2 (range: 247-1,623 cGy/cm^2) by Fernández et al. (49) In another study, the average radiation dose exposure of the reproductive organs during an HSG procedure was found to be 500-1000 mRad (50). An avarage human being has 17,000-20,000 cm^2 surface area and a rat that weighs 250-300 g has 300-400 cm^2 average surface area. In line with these previous studies, we determined the dose that should be applied to rats as 15-20 mRad (9). The development of the first follicular wave in the rodents to the antral follicle occurs in about three weeks. The developmental stage of primordial follicle to secondary follicular may take >30 days (51). Well-developed secondary follicles are observed on the seventh day (52,53).

Pala et al. (9) showed that HSG treatment caused a significant increase in epithelial degeneration in the rat endometrium at three hours after HSG withdrawal. Lee et al. (54) investigated the primary and primordial follicular damage after exposure to gamma radiation in rats and found that the most significant damage occurred after three hours with a reduction after 6-12 hours following radiation exposure. However, Can et al. (19) chose a period of three hours to examine possible acute radiation damage and a period of one month to investigate chronic effects. Our aim was to go further than previous studies. For this reason, we chose a period of seven day to examine possible ionizing radiation and contrast medium damage in the early “acute” period and a six-week period to investigate possible late period ionizing radiation and contrast medium damage. However, for the first time, an experimental model of the HSG process taking the effects of iohexol and ionized radiation separately, on ovarian, fallopian tube and endometrium histopathology are studied. This is the first pilot study in this area and we believe it is a strength of our study. Although, there have been previous studies investigating the damage caused by iodine contrast medium on cells and

tissues, especially the renal tubular system, there is no study that clearly shows its effects on the female internal genital system. Therefore, the effects of iohexol are not as clearly elucidated as those of ionizing radiation. Our current knowledge is limited to research done on other systems. Solomon and Dauerman (55) have investigated the mechanism of action of iodinated contrast agents on the renal tubular system. These authors reported that the mechanisms responsible for the pathogenesis of contrast induced nephropathy are thought to be a combination of the direct tubular toxicity of contrast media, reduction in medullary blood flow, and generation of reactive oxygen species (ROS), in which ROS play a central role (55). ROS can cause vascular endothelial injury and may further intensify tissue parenchymal hypoxia by causing endothelial dysfunction and dysregulation of membrane transport (56-58). Iohexol has high viscosity and osmolality among the low-osmolality contrast media and these characteristics both contribute to cell and tissue toxicity. Iohexol decreases extracellular volume contraction. The direct vasoconstrictor effects of iohexol and further exacerbation of ischemia are significant because the vasoconstricting molecules, including renin, endothelin, and adenosine, increase and the vasodilatory molecules such as prostaglandin and nitric oxide decrease (59). Iohexol is a non-ionic, monomeric, iodinated contrast medium (ICM). Heinrich et al. (60) compared different contrast media with the tetrazolium-based colorimetric assay, and when ICM were compared at equal iodine concentrations (75 mg I/mL), they found that dimeric contrast media showed a slightly weaker effect on inhibition of mitochondrial dehydrogenases than monomers, but this difference was not statistically significant. In the same study, the contrast media were also compared at molar basis and it was shown that dimeric ICM were significantly more cytotoxic than monomers on cultured renal cells (60). Carlisle et al. (61) exposed embryonal cancer cells to iohexol, iopamidol and metrizamide at concentrations below those used for clinical myelography and investigated the outcome using light and electron microscopy. They reported cytologic changes, consisting of swelling and vacuolation of mitochondria and other cytoplasmic organelles, which were observed within one hour of exposure to the contrast media. They observed that after 12 hours, there were changes in shape of cells and cell death. They repeated the study in neuron cultures derived from embryonic stem cells and rat dorsal stem ganglion cell cultures. They reported that iohexol and other iodine contrast media are cytotoxic to cells in culture at less than 20% of the concentration used for myelography and this could contribute to the adverse reactions to myelography seen in people and animals (61). Jensen et al. (62) in their studies with water soluble iodinated contrast agents, the iso-osmolal contrast medium iodixanol was found to be less toxic than iohexol in cultured cells of rat proximal tubule origin. It may be thought that these results suggest that using iodixanol during HSG may be more beneficial but it should not be forgotten that iodixanol is a dimeric form of ICM. Berg et al. (63) showed that iohexol, iodixanol, ioxaglate and diatrizoate all possess antioxidant properties in vitro. The reason for this is unknown, but it is possible, although speculative, that the antioxidant properties of the ICM may contribute to the lower cell death at early time points (63). The results of our study likewise show that all effects, except inflammation, are more severe in the late period. More studies will be required to reach a firm conclusion in this matter. Our results were similar to studies in which ionized radiation was evaluated alone, and ionized radiation together with iodinated contrast agents was evaluated in a particular part of the female genital system, or tissues of other systems. As seen from all studies, both ionizing radiation and iodinated contrast agents cause harmful effects at the cellular level. The results we obtained in our study were in agreement with earlier findings. The point we want to emphasize is that all cellular changes, except inflammation and increased vascularization following inflammation, are present to a greater degree and more severe in the late period. Combined ionizing radiation and iohexol produced more severe cellular changes and a greater increase in reactive oxygen radicals in the tissues examined in our study. The question that needs to be considered here is the necessity of finding methods to protect the reproductive cells of infertile-subfertile women, or to ensure minimal damage during HSG. To mitigate the deleterious effects antioxidant substances may be applied during the process, as in many studies where ionizing radiation and iodinated contrast agent are used together. Pala et al. (9) investigated vitamins C and E for the prevention of endometrial cell damage induced by HSG and reported some success. Yılmaz et al. (20) also contributed to the literature with their studies that pre-HSG melatonin use can protect on ovarian surface epithelium. Gülle et al. (22) proposed different approaches with two different studies. They reported that L-carnitine or Curcumin may be beneficial to protect against the negative effects of ionizing radiation on ovaries (21,22). Can et al. (19) used amifostine to prevent ovarian damage caused by ionizing radiation. Yurut-Caloglu et al. (23) compared the protective roles of L-carnitine and amifostine against radiation-induced acute ovarian damage. Sapmaz et al. (15) examined the effect of trichloroacetic acid attachment and instillation methods on dysplastic changes in ovarian surface epithelium. However, it was reported that more research and studies should be done in all these studies. Kilciksiz and Demirel (11) performed a study using

N-acetylcysteine to prevent the negative effects of ionizing radiation and oxidative stress. Karaman et al. (10) reported that, as a novel approach, agomelatine can be used to prevent nephrotoxicity caused by the use of iodinated contrast media. Duan et al. (24) investigated the protective effect of amlodipine to nephrotoxicity of high- and low-osmolar contrast media. Also, research has been undertaken in the urinary system with the use of theophylline, sodium bicarbonate or similar materials. These findings may be of some relevance in the genital system as there is a shared embryological origin with the urinary system (64). To our knowledge, no proven benefit has been found for the use of other renal protective agents such as N-acetylcysteine, sodium bicarbonate, diuretics, and theophylline in the genital system (65). Sapmaz and Akpolat (8) used lipiodol (iodinated ethyl esters of fatty acids of poppyseed oil) in their studies as a different approach. Lipiodol significantly reduced dysplastic modifications and increased fusiform structures in the myometrium. Lipiodol plus melatonin restored all the negative changes (8). Lipiodol is a water-insoluble iodinated contrast media. It is possible to use both oil and water soluble contrast media during HSG. There are a few differences between the two contrast agents in the evaluation of intra-uterine pathology and in the evaluation of the tubal patency (66). Lipiodol contains mostly linoleic acid and omega series of polyunsaturated fatty acids and it is a potent antioxidant that has many positive effects in the body (67,68). Considering the results of this study, it can be thought that the use of lipiodol may be reasonable. Water-soluble contrast agents are associated with decreased complications and better radiographic quality compared to the lipo-soluble contrast media (69-71). For this reason, hydro-soluble contrast media are widely used during HSG. The result of all these studies is that there is still no definitive optimally safe method for HSG. For now, it seems more logical to use hysterosalpingo-foam sonography (HyFoSy) to evaluate tubal patency (19).

Findings of Dreyer et al. (72) suggested that in case a HyFoSy procedure is performed as the first-line tubal patency test during the fertility work-up, an HSG can be avoided in the vast majority of cases (95% confidence intervals). Perhaps HyFoSy may be considered prior to HSG as a first line assessment. In addition to the previously stated advantages of HyFoSy, the procedure appears to be less expensive than HSG. In general, HyFoSy is a less painful and less time-consuming tubal patency test compared to HSG. It also appears to be an accurate and safe test that can be performed by a single operator in an outpatient clinic setting without the need for radiation exposure, making it a far safer and more patient-friendly first-line tubal patency test (72). Future research should focus on whether tubal patency testing during the fertility workup using HyFoSy leads to the same diagnostic outcomes, subsequent management decisions, and ongoing pregnancy rates as tubal testing using HSG (73,74). To date no large trials have been published comparing HSG with HyFoSy.

Conclusion

As seen in both previous studies and in our study, women are exposed to many harmful agents during HSG. It is therefore important that more benign and patients friendly methods should be investigated and introduced in order to optimise the evaluation of infertile women. For now, first line use of HyFoSy seems advisable with subsequent HSG if necessary, not least because HyFoSy eliminates exposure to ionizing radiation.

Ethics Committee Approval: *This study was performed in the Laboratory Center for Experimental Studies of Çanakkale Onsekiz Mart University with the approval of the University's Laboratory Animals Ethics Committee (approval number: 2016/01-02).*

Informed Consent: *Patient approval has not been obtained as it is performed on animals.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Surgical and Medical Practices: E.P., C.C.G.; Concept: S.H., E.P.; Design: S.H., E.P.; Data Collection or Processing: E.P., C.C.G.; Analysis or Interpretation: E.P., C.C.G.; Literature Search: S.H., E.P.; M.A.Ü., G.A.; Writing: E.P.*

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

Financial Disclosure: *This research was carried out with the support of Çanakkale Onsekiz Mart University Scientific Research Projects Coordination Center. Researchers and authors do not have any financial gain. Çanakkale Onsekiz Mart University Scientific Research Projects Center, which supports the realization of the project, does not have any financial gain.*

References

1. Thoma ME, McLain AC, Louis JF, King RB, Trumble AC, Sundaram R, et al. Prevalence of infertility in the United States as estimated by the current duration approach and a traditional constructed approach. Fertil Steril 2013; 99: 1324-31.e1.
2. Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, Nygren K, et al. International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology. Fertil Steril 2009; 92: 1520-4.
3. Borght MV, Wyns C. Fertility and infertility: definition and epidemiology. Clin Biochem 2018; 62: 2-10.

4. Ludwin I, Ludwin A, Wiechec M, Nocun A, Banas T, Basta P, et al. Accuracy of hysterosalpingo-foam sonography in comparison to hysterosalpingo-contrast sonography with air/saline and to laparoscopy with dye. Hum Reprod 2017; 32: 758-69.
5. Fayez JA, Mutie G, Schneider PJ. The diagnostic value of hysterosalpingography and hysteroscopy in infertility investigation. Am J Obstet Gynecol 1987; 156: 558-60.
6. Roma DA, Ubeda B, Ubeda A, Monzón M, Rotger R, Ramos R, et al. Diagnostic value of hysterosalpingography in the detection of intrauterine abnormalities: a comparison with hysteroscopy. Am J Roentgenol 2004; 183: 1405-9.
7. Copobianco G, Piredda N, Maiore M, Cherchi PL, Dessole M, Virdis G, et al. Hysterosalpingography in infertility investigation protocol: is it still useful? Clin Exp Obstet Gynecol 2015: 42: 448-51.
8. Sapmaz E, Akpolat N. Examination of the effect of pre-Hsg melatonin on endometrial ablation and uterine dysplastic cell development associated with radiation. Fırat Med J 2012; 17: 1-5.
9. Pala S, Atilgan R, Kuloglu T, Kara M, Baspinar M, Can B, et al. Protective effects of vitamin C and vitamin E against hysterosalpingography-induced epithelian degeneration and proliferation in rat endometrium. Drug Des Devel Ther 2016; 10: 4079-89.
10. Karaman A, Diyarbakir B, Durur-Subasi I, Kose D, Özbek-Bilgin A, Topcu A, et al. A novel approach to contrast-induced nephrotoxicity: the melatonergic agent agomelatine. Br J Radiol 2016; 89: 20150716.
11. Kilciksiz S, Demirel C. Oxidative stress, radiation-induced damage and the potential role of N-acetylcysteine as a radioprotector. Turkish J Oncol 2008; 23: 200-7.
12. Bibault JE, Fumagalli I, Ferte C, Chargari C, Soria JC, Deutsch E. Personalized radiation therapy and biomarkerdriven treatment strategies: a systematic review. Cancer Metastasis Rev 2013; 32: 479-92.
13. Liu N, Lei R, Tang MM, Cheng W, Luo M, Xu Q, et al. Autophagy is activated to protect renal tubular epithelial cells against iodinated contrast media induced cytotoxicity. Molecular Medicine Reports 2017; 16: 8277-82.
14. Nieto JJ, Crow J, Sundaresan M, Constantinovici N, Perrett CW, MacLean AB, et al. Ovarian epithelial dysplasia in relation to ovulation induction and nulliparity. Gynecologic Oncology 2001; 82: 344-9.
15. Sapmaz E, Akpolat N. Examination of the effect of trichloroacetic acid attachment and instillation methods on ovarian reserve and dysplastic changes in ovarian surface epithelium. Fırat Med J 2012; 17: 71-5.
16. Goldenberg I, Matetezy S. Nephropathy induced by contrast media: pathogenesis, risk factors and preventive strategies. CMAJ 2005; 17: 1461-71.
17. McCollough PA. Radiocontrast-induced acute kidney injury. Nephron Physiol 2008; 109: p61-72.
18. Haller C, Istvan H. The cytotoxicity of iodinated radiocontrast agent on renal cells in vitro. Invest Radiol 2003; 39: 149-54.
19. Can B, Atilgan R, Pala S, Kuloglu T, Kiray S, Ilhan N. Examination of the effect of ovarian radiation injury induced by hysterosalpingography on ovarian proliferating cell nuclear antigen and the radioprotective effect of amifostine: an experimental study. Drug Des Devel Ther 2018; 12: 1491-500.
20. Yılmaz ES, Sapmaz T, Kazgan H, Yildiz SM, Kocamaz D, Akpolat N, et al. Examination of the antioxidant effects of pre-HSG melatonin use on ovarian surface epithelium in rats: an experimental study. Adv Clin Exp Med 2018; 27: 907-11.
21. Gulle K, Akpolat M, Oz ZS, Bakkal HB, Arasli M, Kokturk F. Protective effect of L-carnitine on morphological alterations and occurrence in developing follicles exposed ionising radiation in rat ovary. J Health Sci 2017; 8: 33-7.
22. Gülle K, Pala I, Akpolat M, Bakkal BH. Protective effect of curcumin on folliculogenesis, and PARP-1 (Poly ADP-ribose polymerase) expression exposed ionising raditation in rat ovary. J Health Sci 2018: 9: 102-11.
23. Yurut-Caloglu V, Caloglu M, Eskiocak S, Tastekin E, Ozen A, Kurkcu N, et al. Comparison of the protective roles of L-carnitine and amifostine against radiation-induced acute ovarian damage by histopathological and biochemical methods. J Cancer Res Ther 2015; 11: 447-53.
24. Duan SB, Liu FY, Luo JA, Wu HW, Liu RH, Peng YM, et al. Nephrotoxicity of high- and low-osmolar contrast media. The protective role of amlodipine in a rat model. Acta Radiol 2000; 41: 503-7.
25. Pouget JP, Mather SJ. General aspects of the cellular response to low and high-LET radiation. Eur J Nucl Med 2001; 28: 541-61.
26. Eric J. Hall, Amato JG. Radiobiology for the Radiologist, Sixth Edition. Lippincott Williams & Wilkins 2006: 135.
27. Li L, Story M, Legerski RJ. Cellular responses to ionizing radiation damage. Int J Radiat Oncol Biol Phys 2001; 49: 1157-62.
28. Little JB. Radiation carcinogenesis. Carcinogenesis 2000; 21: 397-404.
29. Huang L, Grim S, Smith LE, Kim PM, Nickoloff JA, Goloubeva OG, et al. Ionizing radiation induces delayed hyperrecombination in mammalian cells. Mol Cell Biol 2004; 24: 5060-8.
30. Oikawa S. Sequence-specific DNA damage by reactive oxygen species. Environ Health Prev Med 2005; 10: 65-71.
31. Hong WK, Bast RC, Hait WN, Holland JF, Frei E, Frei H. Cancer Medicine. Andreeff M, Goodrich DW, Koeffler P (Ed), Cell Proliferation and Differentiation. USA: Eighth Edition, AACR. 2009: 26-27.
32. Baskar R. Emerging role of radiation induced bystander effects. Cell communications and carcinogenesis. Genome Integr 2010; 1: 13.
33. Diplock AT, Charleux JL, Crozier-Willi G, Kok FJ, Rice-Evans C, Roberfroid M, et al. Functional food science and defence against reactive oxidative species. Br J Nutr 1998; 80(Suppl 1): 77-112.
34. Matés JM. Effect of antioxidant enzymes in the molecular control of reactive oxygen species toxicology. Toxicology 2000; 153: 83-104.
35. Buettner GR, Ng CF, Wang M, Rodgers VGJ, Schafer FQ. A new paradigm: manganese superoxide dismutase influences the production of H2O2 in cells and thereby their biological state. Free Radic Bio Med 2006; 41: 1338-50.
36. Scibior D, Czeczot H. Catalase: structure, properties, functions. Postepy Hig Med Dosw (Online) 2006; 60: 170-80.
37. Mannervik B, Board PG, Hayes JD, Listowsky I, Pearson WR. Nomenclature for mammalian soluble glutathione transferases. Methods Enzymol 2005; 401: 1-8.
38. Hayes JD, Flanagan JU, Jowsey IR. Glutathione transferases. Annu Rev Pharmacol Toxicol 2005; 45: 51-88.
39. Candas R, Sohal S, Radyuk SN, Klickhko VI, Orr WC. Molecularorganization of the glutathione reductase gene in drosophila melanogaster. Arch Biochem Biophys 1997; 339: 323-34.
40. Manisaligil YA, Yurt A. Cellular and molecular effects of ionizing radiation. Duzce Med J 2018; 20: 50-3.
41. Prasad KN. Rationale for using multiple antioxidants in protecting humans against low doses of ionizing radiation. Br J Radiol 2005; 78: 485-9.
42. Tewari S, Khan K, Husain N, Rastogi M, Mishra SP, Srivastav AK. Peripheral blood lymphocytes as in vitro model to evaluate genomic instability caused by low dose radiation. Asian Pac J Cancer Prev 2016; 17: 1773-7.
43. Bulat T, Keta O, Koricanac L, Zakula J, Petrovic I, Ristic-Fira A, et al. Radiation dose determines the method for quantification of DNA double strand breaks. An Acad Bras Cienc 2016; 88: 127-36.

44. Nikitaki Z, Nikolov V, Mavragani IV, Mladenov E, Mangelis A, Laskaratou DA, et al. Measurement of complex DNA damage induction and repair in human cellular systems after exposure to ionizing radiations of varying linear energy transfer (LET). Free Radic Res 2016; 50(Suppl 1): S64-78.
45. Gregoire E, Roy L, Buard V, Delbos M, Durand V, Martin BC, et al. Twenty years of fish-based translocation analysis for retrospective ionizing radiation biodosimetry. Int J Radiat Biol 2018; 94: 248-58.
46. Tello Cajiao JJ, Carante MP, Bernal Rodriguez MA, Ballarini F. Proximity effects in chromosome aberration induction: dependence on radiation quality, cell type and dose. DNA Repair (Amst) 2018; 64: 45-52.
47. Andersen KJ, Vik H, Eikesdal HP, Christensen I. Effects of contrast media on renal epithelial cells in culture. Acta Radiol Suppl 1995; 399: 213-8.
48. Faulhaber O, Bristow RG. Basis of cell kill following clinical radiotherapy. In: Sluyser M, editor. Application of Apoptosis to Cancer Treatment New York: Springer; 2005. p. 293-320.
49. Fernández JM, Vañó E, Guibelalde E. Patient doses in hysterosalpingography. Br J Radiol 1996; 69: 751-4.
50. Shirley LH. Ovarian radiation dosage during histerosalpingogram. Fertil Steril 1971; 22: 83-5.
51. McGee EA, Hsueh AJ. Initial and cyclic recruitment of ovarian follicles. Endocr Rev 2000; 21: 200-14.
52. Mazaud S, Guigon CJ, Lozach A, Coudouel N, Forest MG, Coffigny H, et al. Establishment of the reproductive function and transient fertility of female rats lacking primordial follicle stock after fetal gamma-irradiation. Endocrinology 2002; 143: 4775-87.
53. Gaytán F, Morales C, Bellido C, Aguilar E, Sánchez-Criado JE. Ovarian follicle macrophages: is follicular atresia in the immature rat a macrophage-mediated event? Biol Reprod 1998; 58: 52-9.
54. Lee CJ, Park HH, Do BR, Yoon Y, Kim JK. Natural and radiation-induced degeneration of primordial and primary follicles in mouse ovary. Anim Reprod Sci 2000; 59: 109-17.
55. Solomon R, Dauerman HL. Contrast-induced acute kidney injury. Circulation 2010; 122: 2451-5.
56. Heyman SN, Rosen S, Khamaisi M, Idée JM, Rosenberger C. Reactive oxygen species and the pathogenesis of radiocontrast-induced nephropathy. Invest Radiol 2010; 45: 188-95.
57. Idée JM, Bonnemain B. Reliability of experimental models of iodinated contrast media-induced acute renal failure: from methodological considerations to pathophysiology. Invest Radiol 1996; 31: 230-41.
58. Solez K, Racusen LC, Olsen S. The pathology of drug nephrotoxicity. Journal Clin Pharmacol 1983; 23: 484-90.
59. Solomon R. Contrast media: are there differences in nephrotoxicity among contrast media? BioMed Res Int 2014; 2014: 934947.
60. Heinrich MC, Kuhlmann MK, Grgic A, Heckmann M, Kramann B, Uder M. Cytotoxic effects of ionic high-osmolar, nonionic monomeric, and nonionic iso-osmolar dimeric iodinated contrast media on renal tubular cells in vitro. Radiology 2005; 235: 843-9.
61. Carlisle CH, Pass MA, Lowndes HE, Reuhl KR. Toxicity of the radiographic contrast media iopamidol, iohexol and metrizamide to cell cultures. Vet Radiol Ultrasound 1995; 36: 207-11.
62. Jensen H, Doughty RW, Grant D, Myhre O. The effects of the iodinated x-ray contrast media iodixanol, iohexol, iopromide, and ioversol on the rat kidney epithelial cell line NRK 52-E. Ren Fail 2011; 33: 426-33.
63. Berg K, Skarra S, Bruvold M, Brurok H, Karlsson JO, Jynge P. Iodinated radiographic contrast media possess antioxidant properties in vitro. Acta Radiol 2005; 46: 815-22.
64. Acién P, Acién MI. The history of female genital tract malformation classifications and proposal of an updated system. Hum Reprod Update 2011; 17: 693-705.
65. Beckett KR, Moriarity AK, Langer JM. Safe use of contrast media: what the radiologist needs to know. Radiographics 2015; 35: 1738-50.
66. Piccotti K, Guida D, Carbonetti F, Stefanetti L, Macioce A, Cremona A, et al. Comparison of diagnostic quality in hysterosalpingography between iodinated non-ionic contrast media with low and high osmolarity. La Clinica Terapeutica 2015; 166: e91-7.
67. Abe S, Otsuki M. Styrene maleic acid neocarzinostatin treatment for hepatocellular carcinoma. Curr Med Chem Anti-Canc Agents 2002; 2: 715-26.
68. Brown JM, McIntosh MK. Conjugated linoleic acid in humans: regulation of adiposity and insulin sensitivity. J Nutr 2003; 133: 3041-6.
69. Bhoil R, Sood D, Sharma T, Sood S, Sharma J, Kumar N, et al. Contrast intravasation during hysterosalpingography. Pol J Radiol 2016; 81: 236-9.
70. Fang F, Bai Y, Zhang Y, Faramand A. Oil-based versus water-based contrast for hysterosalpingography in infertile women: a systematic review and meta-analysis of randomized controlled trials. Fertil Steril 2018; 110: 153-60.e3.
71. Nunley WC Jr, Bateman BG, Kitchin JD, Pope TL Jr. Intravasation during hysterosalpingography using oil-base contrast medium-a second look. Obstet Gynecol 1987: 70(3 Pt 1): 309-12.
72. Dreyer K, Out R, Hompes PGA, Mijatovic V. Hysterosalpingo-foam sonography, a less painful procedure for tubal patency testing during fertility workup compared with (serial) hysterosalpingography: a randomized controlled trial. Fertil Steril 2014; 102: 821-5.
73. Emanuel MH, van Vliet M, Weber M, Exalto N. First experiences with hysterosalpingo-foam sonography (HyFoSy) for office tubal patency testing. Hum Reprod 2012; 27: 114-7.
74. Dreyer K, Mijatovic V, Emanuel MH, Hompes PGA. Hysterosalpingo-foam sonography (HyFoSy), a new technique to confirm proximal tubal occlusion after treatment of a hydrosalpinx by an essure device prior to in vitro fertilization (IVF). Fertil Steril 2012; 98: 224.

Fetal cardiac tumors: prenatal diagnosis, management and prognosis in 18 cases

Mustafa Behram[1], Süleyman Cemil Oğlak[2], Züat Acar[1], Salim Sezer[1], Helen Bornaun[3], Aytül Çorbacıoğlu[1], İsmail Özdemir[1]

[1]Clinic of Perinatology, University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Turkey

[2]Clinic of Obstetrics and Gynecology, University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital, Diyarbakır, Turkey

[3]Clinic of Pediatric Cardiology, University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Turkey

Abstract

Objective: To evaluate the long-term follow-up of patients with fetal cardiac tumors (FCTs), and to review the literature regarding advances in diagnosis and management of FCTs in the last decade.

Material and Methods: In this retrospective study, pregnant women referred to a single center maternal-fetal medicine unit between 2013 and 2018 for advanced ultrasonography, were reviewed. Pediatric cardiology counseling was offered to women whose fetuses had FCTs. All patients were evaluated according to revised diagnostic criteria for tuberous sclerosis complex (TSC). Medical treatment was administered to patients with FCTs ≥30 mm or if they were symptomatic. Everolimus therapy at a dose of 2x0.25 mg twice a week for three months was started in the postnatal period.

Results: Out of the 75,312 patients referred 18 (0.024%) were diagnosed with FCTs. Six were referred with fetal arrhythmias and the others were diagnosed with FCTs during routine follow-up. Ten patients (55%) with FCTs were diagnosed with TSC. All tumors were assessed to be rhabdomyoma. Mean tumor diameter in fetuses with TSC was significantly larger than those without TSC (29.8±14.1 mm versus 9.3±4.8 mm, respectively; p=0.004). All patients (n=2) who received medical therapy had a diagnosis of TSC and multiple FCTs and a reduction in tumor size occurred. Tumor size decreased in eight patients spontaneously during follow-up, but increased in one patient who had multiple locations but no TCS. No change in size was observed in the remaining seven cases. None of the fetuses died during the 1-5 year follow-up period.

Conclusion: Rhabdomyoma are usually multiple and associated with TSC. Rhabdomyomas with TSC are larger, but most regress spontaneously or respond well to medical treatment after birth, and have an excellent long-term prognosis. (J Turk Ger Gynecol Assoc 2020; 21: 255-9)

Keywords: Fetal cardiac tumors, rhabdomyoma, tuberous sclerosis

Received: 29 May, 2020 **Accepted:** 14 August, 2020

Introduction

Fetal cardiac tumors (FCTs) are rare, and the incidence of these tumors in different series ranges from 0.08% to 0.27%. This low incidence may be related to the difficulties in ultrasonographic screening. These difficulties may include the tumor being too small or only being seen as an echogenic focus. However, with advances in non-invasive diagnostic methods, such as fetal echocardiography and magnetic resonance imaging in the last decade, the diagnosis of FCTs has become easier. Therefore, in recent years, increasing numbers of patients with FCTs have been identified prenatally (1,2).

FCTs, after excluding pericardial tumors or cysts, can be divided into two groups: benign tumors including rhabdomyomas, teratomas, fibromas, and myxomas; and malignant tumors

Address for Correspondence: *Mustafa Behram*
e.mail: dr.behramgs@gmail.com ORCID: orcid.org/0000-0002-1157-7273

Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2020.2019.0180

including rhabdomyosarcomas and fibrosarcomas (3,4). FCTs, especially rhabdomyomas, are often associated with tuberous sclerosis complex (TSC). FCTs have been reported to be associated with TSC at a rate of 30-50% (5,6). Although most FCTs are benign, they may cause serious complications, such as intracardiac flow obstruction, heart valve insufficiency, rhythm disturbances, heart failure, hydrops fetalis, and even death (7). Conservative treatment or surgical resection may be a treatment option depending on tumor progression, location, number, complications, condition, and extracardiac involvement. However, the conservative approach should be prioritized unless there are severe complications in the fetus. Surgical treatment is suggested only in symptomatic patients with hemodynamically unstable FCTs or life-threatening arrhythmia.

This study aimed to evaluate the long-term follow-up of patients with FCTs who were diagnosed by fetal echocardiography in the prenatal period and to review the literature regarding advances in diagnosis and management of FCTs in the last decade.

Material and Methods

Pregnant women who were referred to the Maternal-Fetal Medicine unit of University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital between 2013 and 2018 for advanced ultrasonography were reviewed in this retrospective study. Data collected included the mean age of the pregnant women, parity, gestational week, gender, and the birth weight of the fetuses. Pediatric cardiology counseling was offered to all pregnant women whose fetuses had FCTs. Serial echocardiography was performed in all patients with active pregnancy management. All patients were evaluated with serial, two-dimensional, color, and pulse wave Doppler echocardiography until delivery. Echocardiography was re-performed by a pediatric cardiologist in all patients with FCTs after birth. The tumor number, location, size, and prognosis of the tumor were documented.

All patients were evaluated according to revised diagnostic criteria and also underwent genetic analysis for TSC (8). The major criteria were facial angiofibroma or forehead plaque, non-traumatic ungual or periungual fibroma, three or more hypomelanotic macules, shagreen patch (connective tissue nevus), multiple retinal nodular hamartomas, cortical tuber, subependymal nodule, subependymal giant cell astrocytoma, cardiac rhabdomyoma, lymphangiomyomatosis, and renal angiomyolipoma. Minor features were multiple, randomly distributed pits in dental enamel, hamartomatous rectal polyps, bone cysts, cerebral white matter radial migration lines, gingival fibromas, non-renal hamartomas, retinal achromic patch, "confetti" skin lesions, and multiple renal cysts. TSC was diagnosed if either two major criteria or one major criterion plus two minor features were present. TSC was also accepted in patients with positive genetic analyses. Moreover, molecular genetic testing was performed to detect *TSC1* and *TSC2* gene mutations for TSC.

Medical treatment was administered to patients with FCTs ≥30 mm or if they were symptomatic. Everolimus therapy at a dose of 2x0.25 mg twice a week for three months was started in the postnatal period and closely monitored by assessing lipid parameters and with echocardiography.

The Local Ethics Committee of University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital approved the study (approval number: 2019/144). We obtained informed consent forms from all participants.

Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). A descriptive statistical analysis was performed. Continuous variables were expressed as mean ± standard deviation or median values, and categorical variables were presented as numbers and percentages. The Kolmogorov-Smirnov test was used to evaluate the distribution of continuous variables, and a paired Samples t-test was used to compare measurements. A p-value of <0.05 was considered statistically significant.

Results

Out of the 75,312 patients referred for advanced ultrasonographic examinations, 18 (0.024%) were diagnosed as having FCTs. The pregnant women whose fetuses had cardiac tumors were often multiparous (11 patients, 61.1%), and their mean age was 29.9±5.2 years. All patients were diagnosed during the fetal period. The median (range) gestational week at diagnosis was 28.5 (20-35) weeks. Out of the 18 patients, six were referred because of fetal arrhythmias. The others were diagnosed as having FCTs during routine ultrasonographic follow-up. None of the patients had fetal extracardiac sonographic findings. Prenatal screening for Down Syndrome was not performed in any patient due to advanced gestational week at the time of presentation. All patients were followed-up monthly during pregnancy.

Eleven (61.1%) of the fetuses diagnosed as having FCTs were male. Also, 10 patients (55.5%) with FCTs were diagnosed as having TSC. The diagnosis of TSC was made by performing a molecular genetic test after birth. Female sex (6 patients) was more common in patients with TSC-diagnosed FCTs. Two patients previously diagnosed as FCT associated with TSC also had autism. The median follow-up was 3.5 years (Table 1).

All patients were evaluated as having rhabdomyomas according to location, echogenicity (nodular hyperechogenicity), and

echotexture. FCTs had multiple locations in 16 patients. 62.5% of these patients were diagnosed as having TSC. The large part of the tumors originated from the left and right ventricles (Table 2). Also, the mean tumor diameter of the fetuses with TSC was significantly larger than those without TSC (29.8±14.1 mm versus 9.3±4.8 mm, respectively, p=0.004).

All patients who received medical therapy had a diagnosis of TSC and multiple FCTs. Two patients who underwent medical treatment, a reduction in tumor size was observed. The tumor size decreased in eight patients spontaneously without a treatment during follow-up and increased in only one patient. However, there were no changes in tumor size in seven patients. In the case of one FCT with multiple locations and without a diagnosis of TSC, tumor size increased. Four patients received antiarrythmic treatment. None of the fetuses died during the follow-up period.

Discussion

In this case series the following findings were observed: (1) the incidence of FCTs was 0.024%; (2) these tumors often had multiple locations and were often associated with TSC; (3) the tumors related to TSC were larger than those with no evidence of TSC; (4) the size of tumors was frequently reduced with medical therapy. Although FCTs are often associated with a benign prognosis, they may cause severe conditions such as hydrops fetalis and may require further intervention. Tumors, especially those located at the level of the atrio-ventricular or semilunar valves, may impair cardiac function (Figure 1).

FCTs are rare, but they may cause serious conditions such as life-threatening arrhythmias, heart failure, or death (9). Therefore, early diagnosis of these tumors is essential. The incidence of FCTs differs across series. In autopsy studies performed in all age groups, FCTs ranged between 0.0017% and 0.28% (10). In a study by Zhou et al. (11), 16,866 fetuses with a high risk of cardiac malformation were evaluated, and the incidence of FCTs was reported to be 0.08%. In our study, the incidence of FCTs was 0.024%. The reason for a lower incidence of FCTs may be the inclusion of all fetuses referred for advanced ultrasonography, not specifically for fetal echocardiography. In addition, variable inclusion criteria, environmental and genetic factors, and regional differences may be the cause for the varying incidences of FCTs.

FCTs are often benign, and malignant tumors are extremely rare. The most common of benign cardiac tumors are rhabdomyomas (60%), teratomas (25%), and fibromas (12%) (3,12). Rhabdomyoma usually presents as a nodular, hyperechogenic mass, often multiple, and is variable in size. Rhabdomyomas can be intramural or intracavitary in any cardiac chamber but often originate from the interventricular septum or right ventricle (12). In our study, all rhabdomyomas, except in two cases, were multiple and were generally located in ventricles and interventricular septa.

Table 1. Demographic features of patients

Patient no.	Sex	Birth weight (g)	TSC	Additional anomalies	Follow-up (year)
1	M	2800			3
2	F	2500	+		1
3	M	2700	+		2
4	M	2600			1
5	F	3130	+		1
6	M	3250			4
7	M	3400	+		3
8	F	2750	+	+ (autism)	4
9	M	2610			5
10	M	3940			5
11	F	3630			4
12	F	3500	+		5
13	M	3200	+		5
14	M	2390			1
15	M	3400	+		3
16	M	2600			1
17	F	2750	+	+ (autism)	4
18	F	3500	+		5

TSC: Tuberous sclerosis complex, M: Male, F: Female

In a study by Lee et al. (13) there were 10 male (58.8%) and seven female (41.2%) newborns among the 17 rhabdomyoma patients. The sex distribution in our case series was very similar to this with 11 fetuses (61.1%) being male.

Rhabdomyomas are thought to be hormone-sensitive tumors, in which a decrease in dimensions is expected in the postpartum period (14). In our study, the dimensions of eight rhabdomyomas with a smaller size decreased spontaneously. However, in two patients, the tumor regressed with medical treatment. These two fetuses, who had life-threatening findings and were not suitable for surgery, were treated with everolimus, the mammalian target of the inhibitor of rapamycin. Rhabdomyomas were usually multiple and were associated with TSC.

Rhabdomyoma related to TSC is generally larger than those without TSC (15,16) as was the case in our patients.

It is widely accepted that the treatment for symptomatic cardiac tumors is surgical. However, because rhabdomyomas are

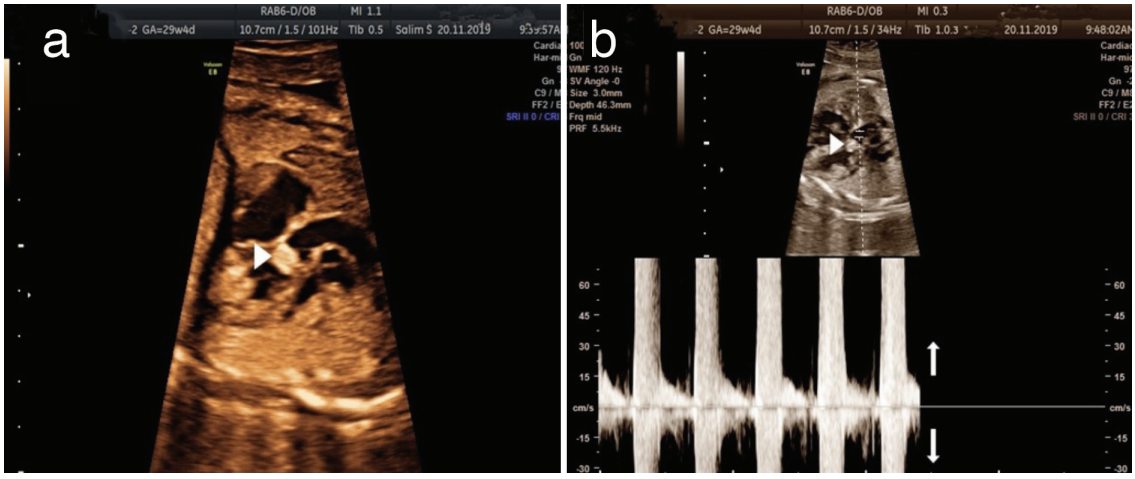


Figure 1. A rhabdomyoma is located at the level of the aortic valve (arrow head) (a). Power Doppler obtained just above the tumor at the beginning of the ascending aorta (b). Bidirectional flow demonstrated aortic regurgitation (arrows)

Table 2. Characteristics of FTCs

Patient no.	TSC	Single or multiple	Tumor location	Largest diameter of tumor (mm)	Medical therapy	Tumor evolution
1		S	LV	11		Pr
2	+	M	LV, RV, IVS	15		St
3	+	M	LV, IVS	30	+	Pr
4		M	LV, RV	6		St
5	+	M	RV	11		Pr
6		M	LV, RV, IVS	10		St
7	+	M	RV	11		Pr
8	+	M	LV, RV	30	+	St
9		M	LV	5		St
10		M	LV, RV	10		St
11		S	LV	7		Pr
12	+	M	LV, IVS	40	+	Pr
13	+	M	RV, IVS	50	+	Pr
14		M	LV, RV	20		Pr
15	+	M	RV	11		Pr
16		M	LV, RV	6		Prog.
17	+	M	LV, RV	30	+	St
18	+	M	LV, IVS	40	+	Pr

FCT: Fetal cardiac tumor, TSC: Tuberous sclerosis complex, S: Single, M: Multiple, LV: Left ventricle, RV: Right ventricle, IVS: Interventricular septum, Pr: Partial regression, Prog: Progression, St: Stable

multiple, localized, and infiltrative, surgical treatment is difficult and should be performed in limited cases. Although the United States Food and Drug Administration has not yet approved the treatment of cardiac rhabdomyomas with everolimus, many rhabdomyoma cases have been medically treated with this agent (17). Rhabdomyomas are benign tumors, and their long-term prognosis is excellent (7). We observed no complications due to cardiac tumors except the presence of hydrops fetalis in one fetus.

Study limitation

The main limitation of the present study is the relatively small sample size. The patients included in our study were followed at a single center.

Conclusion

Rhabdomyoma are usually multiple and associated with TSC. Compared with non-TSC, rhabdomyomas with TSC are larger but most regress spontaneously or respond well to medical treatment after birth. Affected babies have an excellent long-term prognosis.

Ethics Committee Approval: *The Local Ethics Committee of University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital approved the study (approval number: 2019/144).*

Informed Consent: *We obtained informed consent forms from all participants.*

Peer-review: *Externally and internally peer-reviewed.*

Author Contributions: *Surgical and Medical Practices: A.Ç., H.B.; Concept: M.B., Z.A., S.S., İ.Ö.; Design: M.B., S.C.O., H.B., A.Ç.; Data Collection or Processing: M.B., S.S., İ.Ö., H.B.; Analysis or Interpretation: M.B., S.C.O., Z.A., A.Ç., İ.Ö.; Literature Search: M.B., S.C.O., Z.A., S.S.; Writing: M.B., S.C.O.; Critical Review: M.B., S.C.O.*

Conflict of Interest: *The authors report no conflict of interest.*

Financial Disclosure: *This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.*

References

1. Mackie AS, Kozakewich HP, Geva T, Perez-Atayde AR, Mulliken JB. Vascular tumors of the heart in infants and children: case series and review of the literature. Pediatr Cardiol 2005; 26: 344-9.
2. Carrilho MC, Tonni G, Edward Araujo J. Fetal cardiac tumors: prenatal diagnosis and outcomes. Rev Bras Cir Cardiovasc 2015; 30: VI-VII.
3. Isaacs H Jr. Fetal and neonatal cardiac tumors. Pediatr Cardiol 2004; 25: 252-73.
4. Restrepo CS, Vargas D, Ocazionez D, Martínez-Jiménez S, Betancourt Cuellar SL, Gutierrez FR. Primary pericardial tumors. Radiographics 2013; 33: 1613-30.
5. Jóźwiak S, Kawalec W, Dłuzewska J, Daszykowska J, Mirkowicz-Małek M, Michałowicz R. Cardiac tumours in tuberous sclerosis: their incidence and course. Eur J Pediatr 1994; 153: 155-7.
6. Chan HSL, Sonley MJ, Moes CAP, Doneman A, Smith CR, Martin DJ. Primary and secondary tumors of childhood involving the heart, pericardium and great vessels. A report of 75 cases and review of the literature. Cancer 1985; 56: 825-36.
7. Yuan SM. Fetal primary cardiac tumors during perinatal period. Pediatr Neonatol 2017; 58: 205-10.
8. Roach ES, Gomez MR, Northrup H. Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. J Child Neurol 1998; 13: 624-8.
9. Paladini D, Palmieri S, Russo MG, Pacileo G. Cardiac multiple rhabdomyomatosis: prenatal diagnosis and natural history. Ultrasound Obstet Gynecol 1996; 7: 84-5.
10. McAllister HA Jr. Primary tumors of the heart and pericardium. Pathol Annu 1979; 14(Pt 2): 325-55.
11. Zhou QC, Fan P, Peng QH, Zhang M, Fu Z, Wang CH. Prenatal echocardiographic differential diagnosis of fetal cardiac tumors. Ultrasound Obstet Gynecol 2004; 23: 165-71.
12. Niewiadomska-Jarosik K, Stańczyk J, Janiak K, Jarosik P, Moll JJ, Zamojska J, et al. Prenatal diagnosis and follow-up of 23 cases of cardiac tumors. Prenat Diagn 2010; 30: 882-7.
13. Lee KA, Won HS, Shim JY, Lee PR, Kim A. Molecular genetic, cardiac and neurodevelopmental findings in cases of prenatally diagnosed rhabdomyoma associated with tuberous sclerosis complex. Ultrasound Obstet Gynecol 2013; 41: 306-11.
14. Carvalho SR, Marcolin AC, Cavalli RC, Crott GC, Mendes MC, Duarte G, et al. Fetal cardiac rhabdomyoma: analysis of five cases. Rev Bras Ginecol Obstet 2010; 32: 156-62.
15. Jóźwiak S, Kotulska K, Kasprzyk-Obara J, Domańska-Pakiela D, Tomyn-Drabik M, Roberts P, et al. Clinical and genotype studies of cardiac tumors in 154 patients with tuberous sclerosis complex. Pediatrics 2006; 118: e1146-51.
16. Yao L, Chen Y, Wu QQ. Ultrasound diagnosis of fetal cardiac rhabdomyoma and its relationship with nodular sclerosis. Chin J Prenat Med 2002; 5: 168-70.
17. Martínez-García A, Michel-Macías C, Cordero-González G, Escamilla-Sánchez KI, Aguinaga-Ríos M, Coronado-Zarco A, et al. Giant left ventricular rhabdomyoma treated successfully with everolimus: case report and review of literature. Cardiol Young 2018; 28: 903-9.

Robotic versus laparoscopic hysterectomy; comparison of early surgical outcomes

Özgüç Takmaz, Mete Güngör

Department of Obstetrics and Gynecology, Acıbadem Mehmet Ali Aydınlar University Faculty of Medicine, İstanbul, Turkey

Abstract

Objective: To compare early surgical outcomes of robotic assisted laparoscopic hysterectomy with laparoscopic hysterectomy for benign diseases, in terms of operation time, estimated blood loss (EBL), perioperative complications, hospital stay and first gas discharge.

Material and Methods: Medical records of 146 patients who either underwent laparoscopic (n=84) or robotic assisted laparoscopic hysterectomy (n=62) for benign diseases were extracted from records. Demographic characteristics and operation time, EBL, length of hospital stay and first gas discharge were compared between the groups.

Results: Mean age and mean body mass index of both groups were comparable. The difference in the mean EBL was not statistically significant between laparoscopic (91±65 mL) and robotic group (80±37 mL, p=0.43). The difference in the mean first gas discharge time was not statistically different between laparoscopic (15±5 hours) and robotic group (17±6 hours, p=0.33). The length of hospital stay was comparable between groups (1.4±0.5 vs 1.5±0.7 days, p=0.64). The mean operation time was longer for the robotic group (150±180 minimum) when compared with laparoscopic group (105±18 minimum, p<0.01). The mean uterine weight of the robotic group was significantly heavier compared with laparoscopic group (234±157 grams vs 153±119 grams, respectıvely, p<0.01).

Conclusion: Early surgical outcomes of robotic assisted laparoscopic and laparoscopic hysterectomy were comparable in terms of EBL, first gas discharge and hospital stay. Operation time was longer for robotic hysterectomy. (J Turk Ger Gynecol Assoc 2020; 21: 260-4)

Keywords: Robotic hysterectomy, laparoscopic hysterectomy

Received: 19 November, 2019 **Accepted:** 06 February, 2020

Introduction

Hysterectomy is still the second most common gynecologic procedure for benign uterine diseases second to c-section (1). The most common indications for hysterectomy are fibroids and abnormal uterine bleeding (2). Various novel types of medical and surgical treatments have been increasingly implemented in gynecology practice including for hysterectomy. Hysterectomy may be performed with abdominal (AH), vaginal (VH), laparoscopic (LH) and robotic assisted laparoscopic (RH) approaches. An increasing trend for minimally invasive hysterectomy approaches using the latter three techniques, VH, LH and RH, has occurred in the last two decades (3). Compared to AH, minimally invasive hysterectomy procedures provide shorter hospital stay, less bleeding, faster recovery and lower infection rates with better cosmetic results (4,5). As a result, minimally invasive hysterectomy procedures are recommended as the first option when compared with the abdominal route (6). After the Food and Drug Administration (FDA) approval of robotic assisted laparoscopic surgery in gynecologic procedures in 2005, another alternative option was accepted into the range of minimally invasive hysterectomy procedures available. Although RH has disadvantages, such as increased cost and longer operation times, improved dexterity, faster learning curve, instrument facilitation of 7 degrees of freedom, decreased tremor and 3D visualization make RH procedure preferable, especially in more difficult cases such as in morbidly obese patients, having had prior abdominal surgery or patients with an enlarged uterus (7-9).

Address for Correspondence: *Özgüç Takmaz*
e.mail: ozguctakmaz@hotmail.com ORCID: orcid.org/0000-0002-3397-7980

Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2020.2019.0187

In this study retrospective comparison of the perioperative outcomes of patients undergoing either LH or RH patients who had undergone hysterectomy for benign gynecologic indications was investigated.

Material and Methods

Medical records of the patients who underwent RH or LH between January 2015 and June 2018 for benign indications were extracted from the hospital database system. Benign indications consisted of fibroids, chronic pelvic pain, abnormal bleeding or uterine prolapse. The study was approved by institutional review board ethics committee (ATADEK 2019-12). Patients who had a non-gynecologic or gynecologic additional procedure in the same session or who had a history of prior surgery or with chronic non-gynecologic conditions (liver, kidney, pulmonary disease, diabetes) were excluded from the study groups. All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For undergoing surgery written informed consent was obtained from all participants.

Medical records of operation time, estimated blood loss (EBL), length of hospital stay and first gas discharge time were evaluated and compared between the groups. Operation time was defined as the time from intubation to the end of extubation of the patient. EBL was calculated as the difference in fluid volume between irrigation and suction. Hospital stay was defined as the post-operative days passed after surgery until discharge. First gas discharge time was defined as in which hour the first gas discharge was recorded after the surgery. Uterine weight was recorded by weighing the excised uterus in the pathologic examination room immediately after removal.

A Rumi II (Cooper Surgical, Trumbull, CT, USA) uterine manipulator was used in all cases after intubation. All operations were performed in the lithotomy position with steep Trendelenburg (up to 30 degrees) with 13mmHg carbon dioxide pressure.

LH operations were performed via four abdominal ports (10 mm umbilical, 5 mm right, left and suprapubic port), and integrated advanced bipolar and ultrasonic instrument (Thunderbeat-Olympus Corp. of America 3500 Corporate Parkway, Center Valley, PA 18034, U.S.A.) was used for dissecting and vessel sealing.

RH operations were performed with either a da Vinci Si^{R} or da Vinci Xi^{R} (Intuitive Surgical, Inc., Sunnyvale, CA., USA) platform via four abdominal ports which were: for the Si platform - 10 mm umbilical, 8 mm right and left ancillary ports and 12 mm assistant port; and for the Xi platform - 8 mm umbilical, right and left ancillary ports and 12 mm assistant port). Side docking was performed for applying the patient card to abdominal ports in order to manage the uterine manipulator. Monopolar scissors were used for dissection and bipolar fenestrated forceps were used for vessel sealing.

After prophylactic antibiotic administration, all cases underwent the same surgical steps. Following the port placement, firstly the round ligaments were dissected. Then the infundibulopelvic ligaments were dissected and if the patient was under 50 years old, utero-ovarian ligaments were dissected in order to preserve the ovaries. Bilateral uterine arteries were sealed and dissected after skeletonization. After incising the vaginal cuff, hysterectomy tissues were removed through the vagina. Vaginal cuff closures were performed with a 2.0 barbed suture in both groups.

No major complication was recorded during any operation or in the early post-operative periods. After post anesthesia care unit, all patients were followed up in the gynecology inpatient service with administration of a routine post-operative follow up medication consisting of non-steroid analgesics and anti-emetics.

Statistical analysis

The R-3.4.3 programme (R-Core Team. 2017, The R Foundation, https://www.r-project.org/) was used for statistical analysis. Normality assessment was made using the Shapiro-Wilks test. Descriptive statistical methods (mean, standard deviation, median) were used for evaluating the study data. Student's t-test was used to compare normally distributed quantitative variables, while Mann-Whitney U test was used for non-normally distributed variables. The statistical significance level was set at 0.05.

Results

Medical data of 146 patients were extracted for the study groups. Of the 146 patients, 84 (57.5%) underwent LH and 62 (42.5%) underwent RH.

Table 1 shows the demographic and surgical characteristics of the two groups. Mean age and body mass index (BMI) were not significantly different between groups. Operation time was significantly longer in the RH group compared to the LH group (150 min ± 180 vs 105 min ± 18, respectively, $p<0.01$). Uterine weight was significantly higher in RH group than LH group (234±157 vs 153±119 grams, respectively, $p<0.01$). The mean EBL were 80 mL and 91 mL for the RH and LH groups, respectively, which was not significantly different ($p=0.43$). The mean first gas discharge time after the operation in the RH group was 17 hours, while in the LH group it was 15 hours and, again, this was not significantly different ($p=0.33$). The mean hospital stay durations were not statistically different

between the RH group and LH group (1.5±0.7 and 1.4±0.5 days, respectively, p=0.64).

Discussion

In the present study perioperative outcomes for RH were comparable with LH, in terms of bleeding, first gas discharge time and hospital stay in patients who underwent simple hysterectomy for benign conditions. However, operation time was significantly longer in the RH group than the LH group. In addition, uterine weight was significantly greater in the RH group compared to the LH group.

After the first description of total laparoscopic hysterectomy by Reich et al. (10) in 1989, the application of minimally invasive procedures increased in hysterectomy operations. Various studies revealed the advantages of minimally invasive hysterectomy, such as less bleeding, lower peri-operative and post-operative complication rates, shorter hospital stay and shorter post-operative recovery period (11-13). Not only were peri-operative improvements evident, long-term benefits of minimally invasive hysterectomy procedures were also reported (5). Despite the advantages of minimally invasive hysterectomy procedures, some drawbacks, such as a steeper learning curve, increased need for a greater range of equipment and more education for hospital staff in the new techniques, have slowed the acceptance of these procedures into routine practice.

One of the most important improvements in minimally invasive gynecologic surgery was the introducing of robotic surgery. The first reported cases series of RH was published in 2002 (14). Thanks to the endo-wrist movements and three dimensional visualization, robotic surgery is superior to laparoscopic procedures in terms of precise dissection and accurate suturing. A further advantage of RH is the shorter learning curve. Studies have shown that as few as fifty RH procedures are sufficient experience to complete the learning curve for this technique (15,16). In addition, following FDA approval for RH, the widespread acceptance of this technique accelerated (17). However, robotic surgery has some disadvantages. These are longer operation times and higher costs (18-20). Longer operation times are due to the docking procedure, that is the fixation of the robotic arms to the ports. It has been shown that docking times can be reduced with greater experience (21). Increased cost is the other major disadvantage of robotic surgery. The average cost of RH is 1.5-3 times higher than the average cost of the LH (22). Investment in the console, maintenance costs and instrument costs per case are the main three contributors to the increased cost of robotic procedures. However, increase in the frequency of usage and decrease in equipment production costs may reduce the average cost of RH in the long term.

Another disadvantage of RH is the size of the robotic system components. A robotic surgery system has three components; the surgeon console, the patient card and the endoscopic tower. In order to organize and apply these devices effectively, both a large operating room and trained hospital staff are needed. There are also cosmetic disadvantages when using robotic surgery. In robotic gynecological surgery, the upper abdominal or umbilical area has to be used for port placements. Port incisions are also larger than laparoscopic incisions. Goebel and Goldberg (23) suggested that robotic surgery may be less preferable because of the poorer cosmetic outcomes associated with its use.

Although discomfort of the surgeon is not a component of perioperative outcome, it is another disadvantage of robotic surgery. Neck stiffness, and finger and eye fatigue have been reported as common complaints of robotic surgeons (24). However, there is no trial that has compared surgeon discomfort between RH and LH operations.

Hospital stay is another component of the perioperative outcome. Similarly; to previous reports, in our study hospital stay for LH and RH was comparable (25).

Although, no perioperative complication was reported in our study groups, a meta-analysis reported that vaginal cuff dehiscence may be higher in RH (26). However, Scandola et al. (27) reported that RH was associated with lower perioperative complications in terms of vaginal cuff dehiscence. When considering peri-operative and post-operative complications, the vaginal approach may be considered as an alternative minimally invasive technique. A Cochrane analysis of hysterectomy techniques highlighted the fewest intra-operative complications, quickest return to baseline activity, and the fewest number of urinary/bowel dysfunction and dyspareunia issues with the vaginal approach (28).

Table 1. Early surgical parameters and characteristics of groups

	Laparoscopic hysterectomy (n=84)	Robotic hysterectomy (n=62)	p
Age (years)	51±8.2	50±4.5	0.75
BMI (kg/m^2)	25±4.7	27±7.5	0.51
Uterine weight (grams)	153±119	234±157	<0.01
Operation time (minutes)	105±18 [110 (70-140)]	150±180 [120 (60-1,120)]	<0.01
EBL (mL)	91±65	80±37	0.43
First gas discharge (hour)	15±5	17±6	0.33
Hospital stay (day)	1.4±0.5	1.5±0.7	0.64

Data presented as mean ± standard deviation.
BMI: Body mass index, EBL: Estimated blood loss

Despite these disadvantages, there are studies showing that robotic hysterectomy is preferable in some patient groups. Several studies have reported that the use of robotic surgery is more advantageous than laparoscopy, especially in obese patients or those having a large uterus (7,29-31).

Study Limitation

There are some limitations of our study. As our study did not include an AH group, the perioperative improvements of endoscopic methods which were reported in previous studies could not be confirmed. Another limitation is the difference of the uterine weight between the groups. Greater uterine weight may have been a cause of the longer operation times in the RH group in our study but, as reported, RH may be preferable in patients with a larger uterus (7,29-31).

Conclusion

RH did not improve perioperative outcomes in patients who underwent simple hysterectomy for benign conditions in this cohort. As operation times were longer and RH is associated with significantly increased costs, it does not seem reasonable to choose a robotic approach for simple hysterectomy. Our results confirm the American College of Obstetricians and Gynecologists guidelines which recommend vaginal or laparoscopic hysterectomy for simple hysterectomy (32). However, robotic hysterectomy is an important minimally invasive surgical alternative for laparoscopic hysterectomy, depending on the patient's status, especially with regard to patient BMI, the difficulty of the surgery and the preferences of the surgeon.

Ethics Committee Approval: *The study was approved by institutional review board ethics committee (ATADEK 2019-12).*

Informed Consent: *For undergoing surgery written informed consent was obtained from all participants.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Surgical and Medical Practices: M.G.; Concept: M.G., Ö.T.; Design: M.G.; Data Collection or Processing: Ö.T.; Analysis or Interpretation: Ö.T.; Literature Search: Ö.T.; Writing: Ö.T.*

Conflict of Interest: *Authors declare that there is no conflict of interest.*

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

References

1. Whiteman MK, Hillis SD, Jamieson DJ, Morrow B, Podgornik MN, Brett KM, et al. Inpatient hysterectomy surveillance in the United States, 2000-2004. Am J Obstet Gynecol 2008; 198: 34.e1-7.
2. Merrill RM. Hysterectomy surveillance in the United States, 1997 through 2005. Med Sci Monit 2008; 14: CR24-31.
3. Turner LC, Shepherd JP, Wang L, Bunker CH, Lowder JL. Hysterectomy surgery trends: a more accurate depiction of the last decade? Am J Obstet Gynecol 2013; 208: 277.e1-7.
4. Olsson JH, Ellstrom M, Hahlin M. A randomised prospective trial comparing laparoscopic and abdominal hysterectomy. Br J Obstet Gynaecol 1996; 103: 345-50.
5. Nieboer TE, Hendriks JC, Bongers MY, Vierhout ME, Kluivers KB. Quality of life after laparoscopic and abdominal hysterectomy: a randomized controlled trial. Obstet Gynecol 2012; 119: 85-91.
6. Johnson N, Barlow D, Lethaby A, Tavender E, Curr E, Garry R. Surgical approach to hysterectomy for benign gynaecological disease. Cochrane Database Syst Rev 2006: CD003677.
7. Orady M, Hrynewych A, Nawfal AK, Wegienka G. Comparison of robotic-assisted hysterectomy to other minimally invasive approaches. JSLS 2012; 16: 542-8.
8. Alkatout I, Mettler L, Maass N, Ackermann J. Robotic surgery in gynecology. J Turk Ger Gynecol Assoc 2016; 17: 224-32.
9. Varghese A, Doglioli M, Fader AN. Updates and controversies of robotic-assisted surgery in gynecologic surgery. Clin Obstet Gynecol 2019; 62: 733-48.
10. Reich H, DeCaprio J, McGlynn F. Laparoscopic hysterectomy. J Gynecol Surg 1989; 5: 213-6.
11. Garry R, Fountain J, Mason S, Hawe J, Napp V, Abbott J, et al. The evaluate study: two parallel randomised trials, one comparing laparoscopic with abdominal hysterectomy, the other comparing laparoscopic with vaginal hysterectomy. BMJ 2004; 328: 129.
12. Jacoby VL, Autry M, Jacobson G, Domush R, Nakagawa S, Jacoby A. Nationwide use of laparoscopic hysterectomy compared with abdominal and vaginal approaches. Obstet Gynecol 2009; 114: 1041-8.
13. Gobern JM, Rosemeyer CJ, Barter JF, Steren AJ. Comparison of robotic, laparoscopic, and abdominal myomectomy in a community hospital. JSLS 2013; 17: 116-20.
14. Diaz-Arrastia C, Jurnalov C, Gomez G, Townsend C Jr. Laparoscopic hysterectomy using a computer-enhanced surgical robot. Surg Endosc 2002; 16: 1271-3.
15. Sandadi S, Gadzinski JA, Lee S, Chi DS, Sonoda Y, Jewell EL, et al. Fellowship learning curve associated with completing a robotic assisted total laparoscopic hysterectomy. Gynecol Oncol 2014; 132: 102-6.
16. Seamon LG, Fowler JM, Richardson DL, Carlson MJ, Valmadre S, Phillips GS, et al. A detailed analysis of the learning curve: robotic hysterectomy and pelvic-aortic lymphadenectomy for endometrial cancer. Gynecol Oncol 2009; 114: 162-7.
17. Pasic RP, Rizzo JA, Fang H, Ross S, Moore M, Gunnarsson C. Comparing robot-assisted with conventional laparoscopic hysterectomy: impact on cost and clinical outcomes. J Minim Invasive Gynecol 2010; 17: 730-8.
18. Paraiso MF, Ridgeway B, Park AJ, Jelovsek JE, Barber MD, Falcone T, et al. A randomized trial comparing conventional and robotically assisted total laparoscopic hysterectomy. Am J Obstet Gynecol 2013; 208: 368.e1-7.
19. Sarlos D, Kots L, Stevanovic N, von Felten S, Schar G. Robotic compared with conventional laparoscopic hysterectomy: a randomized controlled trial. Obstet Gynecol 2012; 120: 604-11.

20. Lonnerfors C, Reynisson P, Persson J. A randomized trial comparing vaginal and laparoscopic hysterectomy vs robot-assisted hysterectomy. J Minim Invasive Gynecol 2015; 22: 78-86.
21. Martinez-Maestre MA, Gambadauro P, Gonzalez-Cejudo C, Torrejon R. Total laparoscopic hysterectomy with and without robotic assistance: a prospective controlled study. Surg Innov 2014; 21: 250-5.
22. Tapper AM, Hannola M, Zeitlin R, Isojarvi J, Sintonen H, Ikonen TS. A systematic review and cost analysis of robot-assisted hysterectomy in malignant and benign conditions. Eur J Obstet Gynecol Reprod Biol 2014; 177: 1-10.
23. Goebel K, Goldberg JM. Women's preference of cosmetic results after gynecologic surgery. J Minim Invasive Gynecol 2014; 21: 64-7.
24. Lee GI, Lee MR, Green I, Allaf M, Marohn MR. Surgeons' physical discomfort and symptoms during robotic surgery: a comprehensive ergonomic survey study. Surg Endosc 2017; 31: 1697-706.
25. Albright BB, Witte T, Tofte AN, Chou J, Black JD, Desai VB, et al. Robotic versus laparoscopic hysterectomy for benign disease: a systematic review and meta-analysis of randomized trials. J Minim Invasive Gynecol 2016; 23: 18-27.
26. Uccella S, Ghezzi F, Mariani A, Cromi A, Bogani G, Serati M, et al. Vaginal cuff closure after minimally invasive hysterectomy: our experience and systematic review of the literature. Am J Obstet Gynecol 2011; 205: 119.e1-12.
27. Scandola M, Grespan L, Vicentini M, Fiorini P. Robot-assisted laparoscopic hysterectomy vs traditional laparoscopic hysterectomy: five meta-analyses. J Minim Invasive Gynecol 2011; 18: 705-15.
28. Aarts JW, Nieboer TE, Johnson N, Tavender E, Garry R, Mol BW, et al. Surgical approach to hysterectomy for benign gynaecological disease. Cochrane Database Syst Rev 2015; 2015: CD003677.
29. Nawfal AK, Orady M, Eisenstein D, Wegienka G. Effect of body mass index on robotic-assisted total laparoscopic hysterectomy. J Minim Invasive Gynecol 2011; 18: 328-32.
30. Orady ME, Karim Nawfal A, Wegienka G. Does size matter? The effect of uterine weight on robot-assisted total laparoscopic hysterectomy outcomes. J Robot Surg 2011; 5: 267-72.
31. Payne TN, Dauterive FR, Pitter MC, Giep HN, Giep BN, Grogg TW, et al. Robotically assisted hysterectomy in patients with large uteri: outcomes in five community practices. Obstet Gynecol 2010; 115: 535-42.
32. Committee opinion no. 628: robotic surgery in gynecology. Obstet Gynecol 2015; 125: 760-7.

Management of gynecological cancers in the COVID-19 era: a survey from Turkey

Duygu Altın[1], İbrahim Yalçın[2], Ghanim Khatib[3], Mine Dağgez Keleşoğlu[4], Sedat Akgöl[5], Ayşe Büşra Önder[6], İlker Kahramanoğlu[7], Tevfik Güvenal[8], Samet Topuz[9], Fuat Demirkıran[7]

[1]Clinic of Obstetrics and Gynecology, Ordu University Training and Research Hospital, Ordu, Turkey

[2]Clinic of Obstetrics and Gynecology, Şanlıurfa Training and Research Hospital, Şanlıurfa, Turkey

[3]Department of Obstetrics and Gynecology, Çukurova University Faculty of Medicine, Adana, Turkey

[4]Department of Obstetrics and Gynecology, Erciyes University Faculty of Medicine, Kayseri, Turkey

[5]Clinic of Obstetrics and Gynecology, University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Turkey

[6]Clinic of Obstetrics and Gynecology, Bakırköy Dr. Sadi Konuk Training and Research Hospital, İstanbul, Turkey

[7]Department of Obstetrics and Gynecology, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul, Turkey

[8]Department of Obstetrics and Gynecology, Manisa Celal Bayar University Faculty of Medicine, Manisa, Turkey

[9]Department of Obstetrics and Gynecology, İstanbul University İstanbul Faculty of Medicine, İstanbul, Turkey

Abstract

Objective: This study aimed to investigate how gynecologic oncologists modified their patient management during Coronavirus disease-2019 (COVID-19) in Turkey.

Material and Methods: An online survey was sent to gynecologic oncology specialists and fellows in Turkey. It included management questions about strategies for newly diagnosed or recurrent endometrial, cervical, ovarian and vulvar cancer during the pandemic. Participants were asked if treatment of these cancers can be delayed or not and, if yes, the duration of delay.

Results: 32.9% of surgeons prescribed oral or intrauterine progesterone for early stage, low-grade endometrial cancer. Conversely, 65.7% and 45.7% of the most surgeons did not change their management for early stage high-grade and advanced stage endometrial cancers respectively, as they perform surgery. 58% and 67.1% of the surgeons continued to prefer standard surgical treatment for microinvasive and early stage cervical cancers, respectively. Radiotherapy was preferred administered with hypofractionated doses for locally advanced cervical cancer (57.1%). While 67.1% of surgeons operated early stage ovarian cancer patients, 50% administered neoadjuvant chemotherapy (NACT) to all advanced stage ovarian cancers and 50% administered more cycles of NACT in preference to interval debulking surgery. 93.7% of the surgeons responded that treatment should not be delayed beyond eight weeks.

Conclusion: Most Turkish gynecologic oncologists modified their management of gynecologic cancers due to the COVID-19 pandemic. While chemotherapy was preferred for ovarian cancer, postponement of the surgery, with or without non-surgical options, was considered for early stage, low-grade endometrial cancer. Treatment of gynecologic cancers should be decided on a case by case basis, taking into account local COVID-19 infection rates and availability of health facilities. Prognosis is also an important consideration if delay is contemplated. Standard treatment and normal time-frames should be used if possible. If not, a postponement for a maximum of eight weeks or referral to another center were acceptable alternatives. (J Turk Ger Gynecol Assoc 2020; 21: 265-71)

Keywords: COVID-19, gynecologic oncology, survey

Received: 12 May, 2020 **Accepted:** 20 July, 2020

Address for Correspondence: *Duygu Altın*
e.mail: duygualtin@yahoo.com ORCID: orcid.org/0000-0002-9072-9393

Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2020.2020.0071

Introduction

At the end of 2019, a novel type of coronavirus, Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2), was identified as the cause of severe pneumonia in China (1). Since then, with the rapid spread of the Coronavirus disease-2019 (COVID-19) and almost all the countries of the world being affected, the World Health Organization defined the disease as a pandemic in March 2020.

In many countries, most hospital beds were occupied by COVID-19 patients, specialists from all branches were assigned to assist COVID-19 patients and elective surgeries have been limited. The management of cancer patients under these circumstances is controversial. It has been reported that cancer patients are more susceptible to COVID-19 (2). However, delay in treatment may worsen prognosis and chance of cure. Thus the main objective has become to treat cancer patients as quickly as possible while limiting the risk of infection.

Like all cancer patients, gynecologic cancer patients should continue to receive health care during the pandemic. However, clinical management has become more challenging for surgeons, since blood products or intensive care unit (ICU) beds may not be available due to COVID-19. Many organizations and associations issued new guidelines, taking into account the effect of the pandemic, for the management of gynecologic cancers (2,3).

As of 10 May 2020, 138,657 cases of COVID-19 have been reported in Turkey and cases continue to occur with variable incidence. The Turkish Society of Gynecologic Oncology (TRSGO) has issued its recommendations that management of gynecological cancer patients may differ between centers according to available resources (4).

The aim of this study was to investigate how gynecologic oncologists modified their management of gynecologic malignancies during the COVID-19 pandemic in Turkey.

Material and Methods

This study was approved by Ordu University Institutional Review Board (approval number: 2020/77). A questionnaire developed by the TRSGO was sent to gynecologic oncology specialists and trainees working actively at either university hospitals, training hospitals, public hospitals or special clinics across Turkey via the internet. The survey was sent in April 2020, along with an informed consent form. Respondents were able to complete and return the survey online. The questionnaire included how management of endometrial, cervical, ovarian and vulvar cancer changed during the pandemic. Participants were also asked if treatment of these cancers can be delayed or not and, if yes, the duration of delay.

Statistical analysis

Descriptive analyses are presented as numbers and percentages. Chi-square test and Fisher's exact test were used to compare clinico-pathologic characteristics. Values of $p<0.05$ were considered statistically significant. SPSS, version 21.0 (IBM Inc., Armonk, NY, USA) was used for statistical calculations.

Results

The survey was sent to 172 physicians listed in the TRSGO database. Of these, 70 (40.7%) gynecologic oncologists or fellows in gynecologic oncology answered the survey. As seen in Table 1, most of the participants were consultants (n=55, 82.1%) and working at either university or training hospitals (n=58, 82.8%). Almost all of them stated their management had changed after the pandemic and they preferred laparotomy (L/T) to laparoscopy (L/S) (73.9% vs 26.1%). While 27 (38.6%) participants believed the risk of getting infected by COVID-19 was more than 20%, 14 (20%) thought it was less than 5%. The majority of the surgeons (n=49, 70%) expect to get back to normal in 2-5 months.

Endometrial cancer

Table 2 shows the approach to patients who are newly diagnosed with endometrial cancer after COVID-19. While most surgeons delayed the surgery (20%) and preferred

Table 1. Characteristics of participants

Position	
Lecturer, n (%)	29 (43.3)
Specialist, n (%)	26 (38.8)
Fellow, n (%)	12 (17.9)
Center	
University, n (%)	29 (41.4)
Training hospital, n (%)	29 (41.4)
Public hospital, n (%)	5 (7.1)
Private, n (%)	7 (10)
Management changed after COVID-19	
Yes, n (%)	68 (97.1)
No, n (%)	2 (2.9)
Preferred route of surgery,	
Laparotomy, n (%)	51 (73.9)
Laparoscopy, n (%)	18 (26.1)
Estimate of the risk of infection to staf through surgical process, %	
<5%, n (%)	14 (20)
5-10%, n (%)	11 (15.7)
11-20%, n (%)	18 (25.7)
>20%, n (%)	27 (38.6)

medical treatment, either with intrauterine or oral progesterone (32.9%) for early stage low-grade endometrial cancer, staging surgery (65.7%) continued to be the mainstay treatment of early stage, high-grade (grade 3/serous/clear cell, etc.) endometrial cancers. Most surgeons continued to perform standard debulking surgery (45.7%) for advanced stage endometrial cancer but 32.9% chose to administer chemotherapy (CT) instead of surgery during the pandemic.

Cervical cancer

Table 2 shows the approach to cervical cancer patients who are newly diagnosed or in whom disease has recurred after COVID-19. While most surgeons continue to operate (58%) microinvasive cervical cancer, 33.3% delayed the surgery. Likewise, standard surgery (67.1%) and delay (20%) were the two leading responses when asked about their approach to early stage cervical cancer. Primary radiotherapy (RT) or chemo-RT was applied without delay to most of the locally advanced cervical cancer (LACC) patients, but hypo-fractionation of the dose (57.1%) was preferred to standard dose (27.1%), in order to reduce the number of hospital visits. 67.1% of surgeons continued to perform exenterative surgery or administered CT/RT to metastatic or recurrent cervical cancer patients.

Ovarian cancer

67.1% of participants did not change their management (staging surgery) in early stage ovarian cancer. If it was not possible to operate, they mostly (12.9%) referred patients to more suitable cancer centers, rather than administering CT after obtaining tissue biopsy. While 38.6% continue to perform interval debulking surgery (IDS) for patients who had already completed their neoadjuvant chemotherapy (NACT), 50% administered more cycles of CT and 11.4% referred patients to another center. 50% of surgeons administered NACT to all advanced stage ovarian cancers, 20% continued to operate, 17.1% limited cytoreductive surgery indication and the remainder either delayed the operation or referred the patients elsewhere. 32.9% of surgeons administered NACT according to cytology, 15.7% performed diagnostic L/S, and 48.6% referred patients to interventional radiology for tissue biopsy. 2.9% administered NACT if there was a very high suspicion of ovarian cancer without confirmation by cytology or tissue biopsy. While 44.3% continued to operate recurrent ovarian cancer patients who were suitable for surgery, 28.6% administered CT and the rest either delayed the operation or referred the patients elsewhere.

Vulvar cancer

As seen in Table 3, most surgeons either preferred to perform surgery immediately (61.4%) or delay it for a couple of weeks (27.1%) for newly diagnosed, early stage vulvar cancer patients. For advanced stage vulvar cancer, most surgeons (64.3%) did not change their practice.

Participants were asked to score their priority for treatment of each gynecologic cancer from 1 to 5, with 1 the lowest priority and 5 the highest priority. One participant did not answer this part of the questionnaire. Table 4 shows the results.

While continuing to be mindful of disease progression, participants were asked their opinion on the maximum time

Table 2. Management of newly diagnosed endometrial cancer and newly diagnosed or recurrent cervical cancer patients after the pandemic

	Standard treatment (surgery) (n, %)	**Only hysterectomy ± BSO (n, %)**	**IUD/oral progesterone (n, %)**	**RT (n, %)**	**CT (n, %)**	**Delay (n, %)**	**Refer to another center (n, %)**
EC: Early stage, low-grade	20 (28.6)	9 (12.9)	23 (32.9)	0	0	14 (20)	4 (5.7)
EC: Early stage, high-grade	46 (65.7)	5 (7.1)	0	0	1 (1.4)	9 (12.9)	9 (12.9)
EC: Advanced stage	32 (45.7)	2 (2.9)	0	1 (1.4)	23 (32.9)	5 (7.1)	7 (10)
	Standard surgical treatment (n, %)	**Primary (chemo) radiotherapy (n, %)**		**Primary (chemo) radiotherapy with hypofractionation (n, %)**		**Delay (n, %)**	**Refer to another center (n, %)**
CC: Microinvasive	40 (58)	1 (1.4)		NA		23 (33.3)	5 (7.2)
CC: Early stage	47 (67.1)	3 (4.3)		NA		14 (20)	6 (8.6)
CC: LACC	NA	19 (27.1)		40 (57.1)		6 (8.6)	5 (7.1)
CC: Metastatic/recurrent	47 (67.1)			NA		9 (12.9)	14 (20)

EC: Endometrial cancer, CC: Cervical cancer, LACC: Locally advanced cervical cancer, BSO: Bilateral salpingo-oophorectomy, IUD: Intrauterine device, RT: Radiotherapy, CT: Chemotherapy

(in weeks) that treatment can be delayed under COVID-19 conditions. As seen in Table 5, most surgeons thought that treatment should start within eight weeks of diagnosis. It was also evident that respondents believed that treatment should start earlier in advanced stage and/or high-grade cancers compared to early stage and/or low-grade cancers. There were significant differences between answers concerning low- and high-grade early stage endometrial cancers ($p<0.001$), early and advanced stage endometrial cancers ($p=0.024$), early stage and LACC ($p<0.001$), early and advanced stage ovarian cancers ($p=0.039$), and early and advanced stage vulvar cancers ($p=0.014$).

Discussion

With the rapid spread of COVID-19 throughout the world, national health systems of many counties experienced additional stresses. Many countries, including Turkey, took steps to slow the spread of infection. Much elective surgery was suspended to allow resources to be deployed for COVID-19. Despite this situation, it was apparent that clinicians had a duty to continue to provide health care to gynecologic oncology patients.

97.1% of responding Turkish gynecologic oncologists stated their cancer management changed during the pandemic. Surgical treatment remained the gold standard for many types of gynecologic cancers. However, performing surgery may not be possible under pandemic conditions. There are several reasons for this. First, gynecologic oncology patients are generally old and have pre-existing comorbidities such as cardiovascular disease or diabetes mellitus. Therefore, they may need observation in ICU postoperatively. Even a young patient undergoing radical surgery and multiorgan resection may need ICU. Unfortunately, many ICU beds were, and continue to be, occupied by COVID-19 patients. Second, some hospitals ran out of blood and blood products since fewer people made blood donation due to the pandemic. Third, when COVID-19 is more prevalent, COVID-19 patients are hospitalized not only in infectious disease or respiratory disease clinics, but also in any available hospital bed. Many clinics were converted into COVID-19 clinics due to the growing number of infected patients. Lastly, some gynecologic oncologists were recruited to take care for COVID-19 patients (5,6).

The route of surgery was another change during the pandemic. The majority of surgeons (73.9%) preferred L/T rather than L/S because of concern about viral transmission via contaminated aerosol produced from port sites during L/S. To date, there is no evidence to show that the COVID-19 virus speads via laparoscopic smoke plume and this theoretical risk was extrapolated from other viral infections. For example, human immunodeficiency virus (HIV), hepatitis B virus (HBV) and

Table 3. Management of newly diagnosed vulvar cancer patients after the pandemic

	Surgery (n, %)	Primary RT (n, %)	Delay (n, %)	Refer to another center (n, %)
Early stage	43 (61.4)	3 (4.3)	19 (27.1)	5 (7.1)
Advanced stage	45 (64.3)		11 (15.7)	14 (20)
RT: Radiotherapy				

Table 4. Priority of treatment during the pandemic. 1 = lowest priority and 5 = highest priority

	1	2	3	4	5
Early stage, low-grade endometrial cancer	33 (47.8)	15 (21.7)	10 (14.5)	4 (5.8)	7 (10.1)
Early stage, high-grade endometrial cancer	2 (2.9)	14 (20.3)	7 (10.1)	16 (23.2)	30 (43.5)
Advanced stage endometrial cancer	10 (14.5)	11 (15.9)	16 (23.2)	11 (15.9)	21 (30.4)
Microinvasive cervical cancer	18 (26.1)	20 (29)	11 (15.9)	10 (14.5)	10 (14.5)
Early stage cervical cancer	6 (8.7)	10 (14.5)	14 (20.3)	9 (13)	30 (43.5)
Locally advanced cervical cancer	7 (10.1)	14 (20.3)	11 (15.9)	11 (15.9)	26 (37.7)
Metastatic/recurrent cervical cancer	16 (23.2)	11 (15.9)	12 (17.4)	10 (14.5)	20 (29)
Early stage ovarian cancer	6 (8.7)	12 (17.4)	5 (7.2)	18 (26.1)	28 (40.6)
Advanced stage ovarian cancer	12 (17.4)	11 (15.9)	10 (14.5)	10 (14.5)	26 (37.7)
NACT completed ovarian cancer	11 (15.9)	13 (18.8)	13 (18.8)	14 (20.3)	18 (26.1)
Recurrent ovarian cancer	20 (29)	8 (11.6)	20 (29)	6 (8.7)	15 (21.7)
Early stage vulvar cancer	13 (18.8)	13 (18.8)	18 (26.1)	5 (7.2)	20 (29)
Advanced stage vulvar cancer	14 (20.3)	11 (15.9)	16 (23.2)	12 (17.4)	16 (23.2)
NACT: Neoadjuvant chemotherapy					

human papillomavirus (HPV) have been detected in surgical smoke (5-8). Although there are a few cases reporting HPV transmission via surgical smoke, HIV and HBV transmission have not been documented (7,9). In light of this theoretical risk surgeons preferred L/T to minimize exposure to these blood borne pathogens, when possible, although no studies have identified COVID-19 in surgical smoke nor reported transmission of other coronaviruses through surgical smoke.

Performing operations solely using L/T because of this hypothetic risk may result in more surgical complications, such as blood loss, wound infection or atelectasis, longer hospital stay and greater risk of COVID-19 exposure for the patient. Since electrosurgical devices create surgical smoke plumes, they potentially increase viral transmission both in open and minimally invasive surgeries. There is no evidence to prove that infection occurs more often via L/S compared to L/T. Nevertheless, precautions should be taken to minimize this theoretical risk and these should include all operating room personnel being equipped with adequate personal protective equipment, L/S being performed with lower intra-abdominal pressure when possible, use of energy should be minimized and smoke evacuation/filtration should be used (8,10). Therefore, we believe that surgeons should decide the route of surgery on a case by case basis.

Oral progesterone or progesterone releasing IUD is the most common management strategy for early stage, low-grade endometrial cancer amongst Turkish gynecologic oncologists and it is a reasonable alternative to surgery. Several studies have reported 75-80% regression rate with oral progestins in young endometrial cancer patients who want to retain fertility (9-12). Even without progesterone therapy, surgery can be postponed for 1-2 months for low-risk endometrial cancers without loss of cure chance (2). Therefore, surgeons prefer to delay surgery, even if they have available resources for the operation. Conversely, most surgeons continue to operate early stage, high-grade and advanced stage endometrial cancer, since the patient may not be cured as a result of treatment delay. Although only 7.1% of respondents preferred it, simple hysterectomy and bilateral salpingo-oophorectomy ± sentinel lymph node biopsy is another option for high-grade endometrial cancer treatment, as reported by Ramirez et al. (3) that has been shown to reduce operative morbidities.

Surgery is the accepted standard of care for early stage cervical cancer. As such, most Turkish gynecologic oncologists continue to operate microinvasive and early stage cervical cancers. If immediate operation was not possible, operations were delayed, since postponing the surgery for 6-8 weeks has been recommended as acceptable for localized disease during the pandemic (3). Primary (chemo) RT was being instigated without delay for most LACC patients, but hypofractionation of the dose (57.1%) was preferred to standard dose (27.1%), in order to reduce the number of hospital visits.

67.1% of participants perform staging surgery for early stage ovarian cancer. Performing only adnexectomy and deferring the staging surgery for 1-2 months may be another alternative under pandemic conditions (2). The benefit of upfront surgery in advanced stage ovarian cancer is well known and NACT is administered for certain indications (11,13). Despite this, half of Turkish gynecologic oncologists, in keeping with their colleagues worldwide, administer NACT to all patients (12,6). Only 20% perform cytoreductive surgery. The availability of ICU beds and blood products may be the reasoning behind this

Table 5. Responses to the question "How long can treatment be delayed during the pandemic?" Data are given as (n, %)

	<2 w	2-4 w	4-6 w	6-8 w	8-12 w	>12 w
Early stage, low-grade endometrial cancer	28 (40.6)	19 (27.5)	16 (23.2)	17 (24.6)	8 (11.6)	6 (8.7)
Early stage, high-grade endometrial cancer	28 (40.6)	22 (31.9)	12 (17.4)	5 (7.2)	2 (2.9)	0
Advanced stage endometrial cancer	22 (31.9)	27 (39.1)	15 (21.7)	4 (5.8)	1 (1.4)	0
Microinvasive cervical cancer	11 (16.2)	22 (32.4)	16 (23.5)	10 (14.7)	6 (8.8)	3 (4.4)
Early stage cervical cancer	17 (24.6)	33 (47.8)	9 (13)	7 (10.1)	2 (2.9)	1 (1.4)
Locally advanced cervical cancer	25 (36.2)	26 (37.7)	11 (15.9)	6 (8.7)	0	1 (1.4)
Metastatic/recurrent cervical cancer	21 (30.9)	20 (29.4)	19 (27.9)	6 (8.8)	2 (2.9)	0
Early stage ovarian cancer	30 (43.5)	24 (24.8)	10 (14.5)	4 (5.8)	1 (1.4)	0
Advanced stage ovarian cancer	25 (36.2)	20 (29)	18 (26.1)	4 (5.8)	1 (1.4)	1 (1.4)
NACT completed ovarian cancer	19 (27.5)	20 (29)	20 (29)	7 (10.1)	2 (2.9)	1 (1.4)
Recurrent ovarian cancer	17 (24.6)	20 (29)	17 (24.6)	8 (11.6)	4 (5.8)	3 (4.3)
Early stage vulvar cancer	17 (24.6)	27 (39.1)	10 (14.5)	7 (10.1)	6 (8.7)	2 (2.9)
Advanced stage vulvar cancer	22 (31.9)	17 (24.6)	17 (24.6)	9 (13)	3 (4.3)	1 (1.4)

NACT: Neoadjuvant chemotherapy

choice, since the majority of these patients need multiorgan resections. 50% of surgeons administered more than 3-4 cycles of NACT before the IDS, as recommended (2,3). One of the remarkable results of this survey was that 48.6% of surgeons referred patients to an interventional radiologist for tissue biopsy before initiation of NACT. Only 15.7% performed diagnostic L/S, which may be a consequence of concerns about viral transmission during L/S. Although ascites cytology is highly accurate in diagnosing ovarian cancer, 32.9% administer NACT according based on the results of cytology (13-15).

The majority of surgeons treated both early and advanced stage vulvar cancer as they had done prior to the pandemic. This result is unsurprising since surgery is the only treatment option in many cases. When the tumor is small, it has been reported that it is acceptable to postpone surgery for a couple of months (2).

Time is particularly important in the fight against cancer as the chance of achieving a cure can be lost if if the delay is too long. However, due to the pandemic, delay in treatment is currently unavoidable. Therefore, one should always keep in mind which patients will benefit most from treatment, who needs to be treated urgently and who can wait for some time without disease progression. Participants indicated a general belief that timing of treatment is more important for advanced stage and high-grade tumors compared to early stage and low-grade tumors. Hence, a delay in cancer treatment to minimize infection risk is more commonly associated with early stage cancers compared to advanced stage tumors.

This is the first national survey of gynecologic oncologists regarding changes to their practice due to the COVID-19 pandemic. A strength of this study is the inclusion of an homogenous group of gynecologic oncologists who actively work in Turkey. However, as this is a single country survey and only 40.7% of gynecologic oncologists responded, it may limit generalization.

Conclusion

Most gynecologic oncologists have changed their management for gynecologic cancers due to the pandemic. While surgery was postponed and progesterone treatment was preferred in early stage low-grade endometrial cancer, CT came to fore for ovarian cancer. Surgery is performed immediately or with a delay for microinvasive and early stage cervical cancers and hypofractionated dose is preferred for LACC. The number of COVID-19 infected patients and availability of health facilities differ from center to center within Turkey. During the pandemic, treatment for gynecologic cancers should be decided on a case by case basis, taking into account local resource availability and local risk of infection, in conjunction with the chance of achieving a cure. The authors believe that, applying standard treatment when possible and, if not, postponing the treatment for a couple of months in patients in whom it is safe to do so or referral to another cancer center when delay is inadvisable are the best choices at the current time.

Ethics Committee Approval: *This study was approved by Ordu University Institutional Review Board (approval number: 2020/77).*

Informed Consent: *It was obtained.*

Peer-review: *Externally and internally peer-reviewed.*

Author Contributions: *Surgical and Medical Practices: D.A.; Concept: F.D.; Design: T.G., S.T.; Data Collection or Processing: İ.K., S.A.; Analysis or Interpretation: G.K. A.B.Ö.; Literature Search: İ.Y., M.D.K.; Writing: D.A.*

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

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

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel Coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020; 382: 727-33.
2. Akladios C, Azais H, Ballester M, Bendifallah S, Bolze PA, Bourdel N, et al. Recommendations for the surgical management of gynecological cancers during the COVID-19 pandemic - FRANCOGYN Group for the CNGOF. J Gynecol Obstet Hum Reprod 2020; 49: 101729.
3. Ramirez P, Chiva L, Eriksson AG, Frumovitz M, Fagotti A, Gonzalez Martin A, et al. COVID-19 Global pandemic: options for management of gynecologic cancers. Int J Gynecol Cancer 2020; 30: 561-3.
4. Kahramanoglu I, Kelesoglu MD, Gungorduk K, Cuylan ZF, Khatib G, Kandemir S, et al. Management of gynecologic cancers during the COVID-19 pandemic. Ege Klin Tıp Derg 2020; 58: Supp: 24-9.
5. Lambertini M, Toss A, Passaro A, Criscietello C, Cremolini C, Cardone C, et al. Cancer care during the spread of coronavirus disease 2019 (COVID-19) in Italy: young oncologists' perspective. ESMO Open 2020; 5: e000759.
6. Mandato VD, Aguzzoli L. Management of ovarian cancer during the COVID-19 pandemic. Int J Gynaecol Obstet 2020; 149: 382-3.
7. Johnson GK, Robinson WS. Human immunodeficiency virus-1 (HIV-1) in the vapors of surgical power instruments. J Med Virol 1991; 33: 47-50.
8. Chowdhury KK, Meftahuzzaman SM, Rickta D, Chowdhury TK, Chowdhury BB, Ireen ST. Electrosurgical smoke: a real concern. Mymensingh Med J 2011; 20: 507-12.
9. Mallick R, Odejinmi F, Clark TJ. Covid 19 pandemic and gynaecological laparoscopic surgery: knowns and unknowns. Facts Views Vis Obgyn 2020; 12: 3-7.
10. Morris SN, Fader AN, Milad MP, Dionisi HJ. Understanding the "Scope" of the Problem: Why Laparoscopy Is Considered Safe

during the COVID-19 Pandemic. J Minim Invasive Gynecol 2020; 27: 789-91.

11. Yamazawa K, Hirai M, Fujito A, Nishi H, Terauchi F, Ishikura H, et al. Yamazawa K, Hirai M, Fujito A, Nishi H, Terauchi F, Ishikura H, Shozu M, Isaka K. Fertility-preserving treatment with progestin, and pathological criteria to predict responses, in young women with endometrial cancer. Hum Reprod 2007; 22: 1953-8.
12. Yu M, Yang JX, Wu M, Lang JH, Huo Z, Shen K. Fertility-preserving treatment in young women with well-differentiated endometrial carcinoma and severe atypical hyperplasia of endometrium. Fertil Steril 2009; 92: 2122-4.
13. Coleridge SL, Bryant A, Lyons TJ, Goodall RJ, Kehoe S, Morrison J. Chemotherapy versus surgery for initial treatment in advanced ovarian epithelial cancer. Cochrane Database Syst Rev 2019: CD005343.
14. Freedman OC, Dodge J, Shaw P, Oza AM, Bernadini M, Kalchook S, et al. Diagnosis of epithelial ovarian carcinoma prior to neoadjuvant chemotherapy. Gynecol Oncol 2010; 119: 22-5.
15. Baransi S, Michaan N, Gortzak-Uzan L, Aizic A, Laskov I, Gamzu R, et al. The accuracy of ascites cytology in diagnosis of advanced ovarian cancer in postmenopausal women prior to neoadjuvant chemotherapy. Menopause 2020; 27: 771-5.

Gynecological cancers and the global COVID-19 pandemic

Ibrahim Alkatout[1], Mojgan Karimi-Zarchi[2], Leila Allahqoli[3]

[1]Department of Obstetrics and Gynecology, University Hospitals Schleswig-Holstein, Kiel School of Gynaecological Endoscopy, Kiel, Germany

[2]Department of Gynecology Oncology, Firoozgar Hospital, Iran University of Medical Sciences, Tehran, Iran

[3]Iran University of Medical Sciences, Tehran, Iran

Abstract

Coronavirus disease-2019 (COVID-19) has reduced the availability of health resources which will affect treatment of gynecological cancers. The present study aimed to provide a treatment protocol for patients with gynecological cancers during the global COVID-19 pandemic. International databases with keywords of COVID-19; Severe Acute Respiratory Syndrome; Middle East Respiratory Syndrome; gynecologic cancer; cervical cancer; and vaginal cancer, vulvar cancer, ovarian cancer, endometrial cancer, tumor, elective surgery, chemotherapy, radiotherapy, cancer, guideline, guidance, women, management, outpatient clinic visits, and triage were comprehensively searched. All the obtained guidelines were studied and the contents were summarized. During the COVID-19 pandemic, early stage endometrial cancer was preferably treated with hormone therapy while radiotherapy was given in preference in later stages. Cervical intraepithelial neoplasia 3 and high-grade squamous intraepithelial lesions should be treated immediately after diagnosis using at least a loop electrosurgical excision procedure while any major surgery should be postponed by 10-12 weeks. In the early stage of cervical cancer, surgery may be delayed by 2-4 weeks, and radiotherapy prescribed for the intervening period. In cases of an ovarian mass with negative tumor markers, no sign of cancer on imaging investigations, no ascites, a low serum CA-125 level, and no papillary projection or vegetation in the base of the cyst, the patient may be given hormone therapy for 2-3 months. In cases of newly diagnosed confirmed ovarian cancers, surgery should be performed as early as possible (maximum: 2-3 weeks). Vulvar and vaginal cancers can be treated within 10-12 weeks of diagnosis, but radiotherapy should be given in preference in this situation. A molar pregnancy is an oncological emergency for which a suction curettage is mandatory; the patient must be monitored for metastases. Information concerning the choice between open or laparoscopic surgery is limited. Given that any patient may be an asymptomatic carrier of the coronavirus, major surgery should be preceded by chest computerized tomography, with and without contrast medium, in order to detect lung lesions. Evidence concerning these recommendations is limited because of the novel and unknown nature of the COVID-19 pandemic. Furthermore, data pertaining to ethical debates about delayed treatment and treatment approaches deviating from current guidelines are also limited. (J Turk Ger Gynecol Assoc 2020; 21: 272-8)

Keywords: COVID-19, gynecological cancer, oncology, elective surgery, chemotherapy, radiotherapy

Received: 13 July, 2020 **Accepted:** 13 October, 2020

Introduction

The coronavirus is a major pathogen that appears to primarily targets the human respiratory system. Previous outbreaks of coronaviruses (CoVs) include the Severe Acute Respiratory Syndrome-CoV (SARS-CoV) and the Middle East Respiratory Syndrome-CoV (MERS-CoV), which were identified as a major threat to public health (1). Older adults and persons of any age with a serious underlying medical condition are at high risk of severe illness from Coronavirus disease-2019 (COVID-19) (2). Treatment for gynecological cancer may weaken the immune system (immunocompromised) and this makes the patients a "high-risk" group for severe effects of COVID-19 (3,4). We lack sufficient information about the diagnosis of cancer, its surgical treatment, chemotherapy, and radiotherapy in patients with an immune deficiency during the global COVID-19 pandemic

Address for Correspondence: *Mojgan Karimi-Zarchi*
e.mail: karimizarchi.m@iums.ac.ir ORCID: orcid.org/0000-0002-8734-9971

Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2020.2020.0119

(5). In addition, medical staff are not trained in counseling patients about the subject. Ethical issues concerning delayed treatment and using therapeutic approaches that deviate from current guidelines are also unresolved (6). The benefits of delaying or modifying treatment must be weighed against the risks of proceeding with regular treatment (3,7-10). Future studies in cancer patients during any emergency situation that availability of health care resources is limited are still vital (5,9). The aim of the current review was to address all existing protocols concerning this issue and provide a well-rounded approach towards the treatment of patients with gynecological cancers during the COVID-19 global pandemic or any similar emergency situation.

Data sources

We performed a comprehensive review of international databases, including Science Direct, PubMed, Cochrane Library, Scopus, and Google Scholar. Keywords used in the searches were: COVID-19; SARS; MERS; gynecologic cancer; cervical cancer; and vaginal cancer, vulvar cancer, ovarian cancer, endometrial cancer, tumor, elective surgery, chemotherapy, radiotherapy, cancer, guideline, guidance, women, management, outpatient clinic visits, and triage. In view of the limited period of time since the start of the COVID-19 pandemic and the absence of extensive information, we took the early guidelines published in various countries and expert opinions into account. The current recommendations are based on existing evidence and may need to be updated as more information or national/international guidelines become available.

General planning of cancer treatment during the COVID-19 pandemic

- The following criteria apply to cancer patients with a high risk of severe complications during the pandemic: age ≥65 years, patients of any age with cardiovascular or pulmonary disease or diabetes, an Eastern Cooperative Oncology Group status ≥2, and those receiving systemic chemotherapy (11).
- In general, it would be reasonable to perform surgery when the patient's survival is expected to be >12 months, the patient does not respond to other alternative treatments, and survival would be compromised if surgery were to be delayed (12,13).
- Whenever non-surgical approaches such as radiotherapy or neoadjuvant chemotherapy can be used instead of surgery, it would be advisable to delay surgery, provided the patient has ready access to the intensive care unit (ICU) and other hospital facilities (14).
- Elective operations for benign conditions should not be performed during the pandemic. If possible, the patients should be given alternative medical treatment to minimize their symptoms and encouraged to stay at home rather than in the hospital (15).
- In times of crisis, healthcare providers should be able to focus their attention and resources on the care of persons severely affected by the coronavirus (15).
- Legally, the patients and their families must be fully informed about the delay in surgery or the use of non-surgical treatment, and the circumstances must be carefully recorded in the informed consent form (12,13).
- Decisions should be made on the basis of weekly tumor boards by a multidisciplinary team (MDT) (12,13,16).
- Both medical staff and patients are at risk of being infected by COVID-19 during cancer treatment (15).

Outpatient management and gynecological oncology clinics

- Patients should be screened on the telephone about COVID-19 symptoms. At the subsequent personal meeting, their body temperature should be measured if possible (12).
- Visits should be restricted to new patients, absolutely essential consultations to address acute oncologic issues, and patients undergoing active treatment for their disease (molar pregnancies and symptomatic patients with cancer recurrence) (12,17,18).
- In cases of patients residing in a different town or city, imaging and laboratory studies should be performed at their residential locations and sent to the treating physician electronically, who then decides about the appropriate treatment (12).
- The number of persons accompanying the patient should be reduced to one. Furthermore, when the patient needs help due to physical or psychological limitations, it should be ensured that the accompanying person is not suspected of having COVID-19 and is not in contact with any person suspected of being infected by the virus (12,17).
- Physical distance should be maintained in the waiting room. The attendance of patients should be planned carefully to prevent crowding (12,13).
- All routine follow-up/surveillance visits should be postponed, or the consultations should be performed via telemedicine or the Internet - if resources permit - until the crisis has stabilized and one may return to the usual operating procedures (18).
- Screening procedures such as mammography and Pap smears should be delayed. If the patient needs to be followed up (within a period of 3 to 6 months), one should opt for the outer time limit (6 months) (12).
- Any intervention that is not absolutely essential should be postponed, such as routine imaging studies or serum markers,

in patients who are asymptomatic and have no evidence of disease at the most recent evaluation (17).

Management of gynecological oncologic diseases

The National Health Service in England states that individual patient decisions must be made by MDTs (14,15). Patients should be prioritized for surgery on the basis of age, comorbidities, family history of cancer, physical aspects, radiological findings, tumor markers (19), and the risk of needing ICU treatment (17). The priority of timing of gynecological cancer surgery under pandemic conditions (COVID-19) or any emergency situation is summarized in Table 1.

Specific considerations for the treatment of gynecological cancer during COVID-19

Surgery should be postponed during the COVID-19 pandemic because of the risks of surgery, anesthesia, the possibility of the patient being an asymptomatic carrier, and developing symptoms postoperatively. It will be difficult to determine whether the complications and lung lesions are caused by the coronavirus or by surgery (4). The existing evidence indicates that, during the COVID-19 pandemic and other global emergencies, clinicians will have to align their treatment of gynecological cancers to the risk-benefit ratio. Specific considerations for treatment during the COVID-19 pandemic or any emergency situation are summarized in Table 2.

General recommendations for surgery during the COVID-19 pandemic:

- Make sure you speak to the patient about the possibility of a COVID-19 infection and its consequences (12).
- The virus could be transmitted to the staff during open surgery or laparoscopy (12).
- The patient should undergo a COVID-19 test before surgery (7,15). In the event of a positive test, surgery should be postponed to after recovery (17).
- During the COVID-19 pandemic, any oncology surgery with the risk of bleeding, infection, and the possibility of requiring ICU should be postponed until appropriate conditions prevail and the required facilities are available (20).
- If possible, intubation and extubation should be performed in a room with negative pressure (12).
- Operating rooms used for patients with suspected COVID-19 should be separate from those for other patients and should be properly ventilated. If possible, patients with COVID should be given operating rooms with negative ventilation (15).
- Only the main staff should be involved in the surgery, except in emergencies. Staff should not be replaced during the operation (13).
- All employees should use personal protective equipment (PPE), such as gowns and protective shields. Wearing and removing PPE must be performed fully in accordance with the existing health recommendations (12).
- Electrosurgery tools should be used with the minimum power setting of the device, and their use should be minimized because they generate particle aerosols.
- Surgical instruments used in patients with suspected COVID-19 should be washed and sterilized separately from other instruments.
- In persons with suspected or confirmed COVID-19, procedures that cause aerosols, such as intubation and extubation, bag-masking, or electrocautery, should be performed under full personal protection (PPE, including mask N95).
- Operating theatres used for emergency surgery should be separated from that of elective surgeries (12).
- Information concerning the preferred choice between open or laparoscopic surgery is limited. In gynecological emergencies and cancer, laparoscopic surgery would be advantageous to the health system in terms of reducing the duration of hospital stays (12). The release of CO_2 should be minimized during laparoscopic surgery (15). The approach that provides maximum safety to the patient and staff and also ensures the shortest operating time should be given preference.
- Given that patients with gynecological cancer may be asymptomatic carriers of the coronavirus, it is best if major surgeries, such as ovarian and endometrial cancer, a real-time reverse transcription polymerase chain reaction (rRT-PCR) test from a throat swab or preferably computed tomography (CT)-thorax with and without contrast should be performed to diagnose lung lesions (20).
- Evidence about COVID-19 is still limited because of the novel and unknown nature of the disease. Medical staff (doctors, nurses, technicians, etc.) as well as patients lack clear data on the subject (21).

Conclusion

- Any delay in gynecological procedures that could exert a negative effect on the patient's health and safety should be avoided. Obstetricians, gynecologists, and other health care practitioners should be aware of the unintentional impact of policies regarding COVID-19, including limited access to time-sensitive obstetric and gynecological procedures.
- Cancer patients bear a higher risk from infection with SARS-CoV-2 than the general population. The risk of severe respiratory complications is high in cancer patients with SARS-CoV-2, who may then require treatment in the ICU.

- The risk of respiratory complications is associated with a history of chemotherapy or surgery in the month preceding the COVID infection (this factor concerns the large majority of cancer patients).
- In cases of life-threatening diseases such as severe hemorrhage in endometrial cancer, surgery - if possible by the minimally invasive approach - should be performed as early as possible.
- In cases of molar pregnancies or newly recognized ovarian cancers, which are gynecological emergencies, surgery is best performed by experienced oncologists; the surgeon should select the simplest type of operation with the minimum operating time and complications.
- In non-emergency cancers, surgery may be delayed for at least 10-12 weeks.
- In cases of cancers that can be treated with radiotherapy, the latter should be started and surgery postponed.
- Given that patients with gynecological cancer may be asymptomatic carriers of the coronavirus, any major surgery such as that for ovarian or endometrial cancer should be preceded by a rRT-PCR test, or preferably a CT of the chest with and without contrast in order to detect lung lesions.
- Ethical issues concerning the use of treatment that differs from current guidelines warrant further investigation.

Table 1. The priority of surgical timing in patients with gynecological cancer during the COVID-19 pandemic (12)

Priority levels cancer	Urgent/emergent (immediate)	Elective surgery delayed for 2-4 weeks	Surgery delayed for 10-12 weeks
Endometrial cancer	1. Patients with life-threatening bleeding who do not respond to protective therapy.	1. High-grade and high-risk cancer. 2. Grade 1 cancer and contraindication for hormone therapy. 3. Diagnostic measures: dilatation and curettage hysteroscopy.	1. Early stages with low-grade disease. 2. Hysterectomy for precancerous diseases including. Complex atypical hyperplasia/ endometrial intraepithelial neoplasia.
Cervical cancer	1. Life-threatening bleeding and failure to respond to radiotherapy.	1. Early stage of cervical cancer.	1. Cervical intraepithelial neoplasia 2,3. 2. Ambiguous colposcopy of the cervix. 3. Microscopic cervical cancer with the mass completely removed by conization 4. Adenocarcinoma *in situ*.
Ovarian cancer	1. Torsion or rupture of a malignant or suspicious pelvic mass. 2. Peritonitis. 3. Intestinal perforation. 4. A leak in the anastomosis. 5. Acute mechanical obstruction of the intestines.	1. Stage 1 and 2 ovarian cancer. 2. Debulking surgery after 6 cycles of chemotherapy.	1. Benign masses or ovarian cysts.
Vulvar and vaginal cancer	-	1. Resection of vulvar tumor.	Vulvar and vaginal intraepithelial neoplasia 2,3.
Gestational trophoblastic disease	1. Severe bleeding that requires hysterectomy. 2. Uterine curettage of molar pregnancy without bleeding.	-	-

COVID-19: Coronavirus disease-2019

Table 2. Specific considerations for the treatment of gynecological cancer during the COVID-19 pandemic (7,12-17,20,22-29)

Endometrialcancer	Low-risk endometrial cancer (grade 1):	Surgical treatment could be delayed by 10-12 weeks, regulatory treatment with systemic hormone therapy - megestrol (160 mg) + GnRHa (3.75 mg) given every 28 days for three months. Curettage should then be repeated or IUD levonorgestrel could be used.
	High-risk endometrial cancer	Surgical treatment can be delayed for 2 - 4 weeks from the time of diagnosis.
	Endometrial cancers in the presence of comorbidities	Systemic hormone therapy, IUD levonorgestrel or radiotherapy.
Cervical dysplasia & cancer	CIN 1 & LSIL	Do not require treatment; the patient should be followed up for 3 to 6 months.
	CIN 2	Can be treated with laser ablation in the clinic.
	CIN 3 & HSIL	At least LEEP should be performed immediately after the diagnosis; conization and major surgery should be deferred for 10-12 weeks.
	Microscopic cervical cancer	If the tumor has been completely removed by conization, surgery should be delayed for 10-12 weeks.
	Early stage of cervical cancer	Surgery can be delayed for 2-4 weeks and radiotherapy may be used. When available, radical radiotherapy should replace surgery. Definitive radiotherapy should be given preference over radical surgery. Tip 1: Definitive radiotherapy and intrauterine therapy; no delay permitted. Tip 2: If the choice is definitely surgery, such as in cases of young patients or those who wish to retain their ovarian function, radical surgery could be delayed for 6-8 weeks, provided the disease is localized by imaging procedures. In those undergoing surgery, SLNB should be performed if possible.
	Locally advanced cervical cancer	Radiotherapy (without delay).
	Cervical cancer stage 4 or recurrent disease	Palliative chemotherapy.
Ovarian mass and cancer	Ovarian mass	In the presence of negative tumor markers, no sign of cancer on imaging procedures, no ascites, a low serum CA-125 level (less than 200 U/mL and 35 U/mL in women of reproductive age and menopausal women, respectively), no papillary projection or vegetation in the base of cyst, one may prescribe hormone therapy with GnRHa (3.75 mg) and/or megestrol (40 mg) or OCPs for 2-3 months. This should be followed by repeat imaging investigations for re-evaluation.
	Newly diagnosed ovarian cancers	Patients with cancer based on imaging procedures and tumor markers should undergo surgery as early as possible (maximum: 2-3 weeks). Radiological grading is recommended as the first step. Patients in stages 1 or 2 should undergo surgery. Patients with stage 3 disease or worse should be given neoadjuvant chemotherapy with carboplatin alone or in combination with paclitaxel. Prior to chemotherapy, malignant disease should be confirmed by obtaining an image-guided biopsy or preferably a cytological examination.
	Patient receiving neoadjuvant therapy	Medical decisions in these patients is highly dependent on hospital resources. Six cycles of neoadjuvant chemotherapy would be better than three. However, it should be noted that additional cycles of chemotherapy increase bone marrow suppression as well as the risk of COVID-19 infection. - In patients who have undergone 6 cycles of neoadjuvant chemotherapy, surgery is best performed 2-4 weeks after the end of chemotherapy.
	Patients receiving adjuvant chemotherapy	Chemotherapy should ideally be concluded earlier than planned. Six cycles of adjuvant chemotherapy have not been proven superior to five.

Table 2. Continued

Ovarian mass and cancer	Patients with recurrence of ovarian cancer	- If secondary surgical cytoreduction is not expected to prolong survival, the patient should be given chemotherapy. Excepted from this are patients who need surgery to alleviate their symptoms. - In these patients, the decision regarding chemotherapy should be based on clinical judgment, the probability of benefits to the patient, and the expected response to existing medication.
	Systemic treatment of germ-cell tumor	- The treatment should be aimed towards a complete cure. - Chemotherapy after surgery should not be given to patients with stage 1; exceptions are those cases in which the decision is made on a multidisciplinary basis. - First- and second-line treatment for the metastatic disease should be stopped only if the decision is made on a multidisciplinary basis. - Instead of high doses, the usual doses can be used to treat these patients.
Vaginal and vulvar intraepithelial neoplasia	VAIN/VIN 2, 3	Resection should be delayed for 10-12 weeks.
	Vulvar cancer	Surgery can be delayed from the time of diagnosis to 2-4 weeks. This method may be used if SLNB is possible. Radical radiotherapy or neonatal chemotherapy, if available, may replace primary surgery.
	Advanced stage of vulvar cancer or recurrent disease	The first-line treatment is palliative chemotherapy.
Molar pregnancy		This condition is an oncological emergency. Suction curettage must be performed and the patients must be followed up for metastasis.

GnRHa: Gonadotropin-releasing hormone agonist, IUD: Intrauterine device, CIN: Cervical intraepithelial neoplasia, LSIL: Low-grade squamous intraepithelial lesion, HSIL: High-grade squamous intraepithelial lesion, LEEP: Loop electrosurgical excision procedure, SLNB: Sentinel lymph node biopsy, OCPs: Oral contraceptive pills, VAIN/VIN: Vulvar and vaginal intraepithelial neoplasia, COVID-19: Coronavirus disease 2019

Acknowledgement: *We gratefully acknowledge the Iranian Society of Gynecology Oncology for their assistance.*

Peer-review: *Externally peer-reviewed.*

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

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

References

1. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun 2020; 109: 102433.
2. CDC. People with certain medical conditions. 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html
3. CDC. People at increased risk for severe illness. 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-higher-risk.html
4. Bizzarri M, Laganà AS, Aragona D, Unfer V. Inositol and pulmonary function. Could myo-inositol treatment downregulate inflammation and cytokine release syndrome in SARS-CoV-2? Eur Rev Med Pharmacol Sci 2020; 24: 3426-32.
5. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol 2020; 21: 335-7.
6. Alkatout I. Communicative and ethical aspects of physician-patient relationship in extreme situations. Wien Med Wochenschr 2015; 165: 491-8.
7. FIGO. COVID-19 & Management of gynecological cancers. Available at: https://www.figo.org/covid-19-management-gynecological-cancers
8. Chen Y, Li L. SARS-CoV-2: virus dynamics and host response. Lancet Infect Dis 2020; 20: 515-6.
9. Carugno J, Di Spiezio Sardo A, Alonso L, Haimovich S, Campo R, De Angelis C, et al. COVID-19 pandemic. Impact on hysteroscopic procedures: a consensus statement from the Global Congress of Hysteroscopy Scientific Committee. J Minim Invasive Gynecol 2020; 27: 988-92.
10. Franchi M, Del Piccolo L, Bosco M, Tosadori C, Casarin J, Lagana AS, et al. Covid-19 and mental health in the obstetric population: a lesson from a case of puerperal psychosis. Minerva Ginecol 2020. doi: 10.23736/S0026-4784.20.04606-7
11. WHO. Report of the who-china joint mission on coronavirus disease 2019 (covid-19). 2020. Available at: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf
12. Iranian Society of Gynecology Oncology. Treatment of patients with gynecological cancers in coronavirus (COVID-19) pandemic conditions in Iran. 2020.
13. The British Gynaecological Cancer Society (BGCS). Framework for care of patients with gynaecological cancer during the COVID-19 pandemic. 2020. Available at: https://www.bgcs.org.uk/wp-content/uploads/2020/03/BGCS-covid-guidance-v1.-22.03.2020.pdf
14. Webmaster S. Sages recommendations regarding surgical management of gastric cancer patients during the response to the covid-19 crisis. 2020. Available at: https://www.sages.org/sages-recommendations-surgical-management-gastric-cancer-covid-19-crisis/
15. European Society of Gastrointestinal Endoscopy (ESGE). Recommendations on gynaecological laparoscopic surgery during Covid-19 outbreak. 2020. Available at: https://esge.org/wp-content/uploads/2020/03/Covid19StatementESGE.pdf

16. Clinical guide for the management of essential cancer surgery for adults during the coronavirus pandemic. 2020. Available at: https://www.asgbi.org.uk/userfiles/file/covid19/c0239-specialty-guide-essential-cancer-surgery-coronavirus-v1-70420.pdf
17. Ramirez PT, Chiva L, Eriksson AGZ, Frumovitz M, Fagotti A, Gonzalez Martin A, et al. COVID-19 global pandemic: options for management of gynecologic cancers. BMJ 2020; 30.
18. Huntsman Cancer Institute patient scheduling recommendations during COVID-19 crisis. 2020. Available at: https://www.nccn.org/covid-19/pdf/HCI_Patient_Scheduling_Recs_during_COVID.pdf
19. National comprehensive cancer network (NCCN). NCCN Clinical Practice Guidelines in Oncology. 2019.
20. European Society of Gynaecological Oncology (ESGO). Management of uterine cancer during the COVID-19 pandemic. 2020. Available at: https://eacademy.esgo.org/esgo/2020/covid-19/293201/session.speakers.management.of.uterine.cancer.during.covid-19.pandemic.html?f=listing%3D3%2Abrowseby%3D8%2Asortby%3D2%2Amedia%3D1%2Alabel%3D19832%2Afeatured%3D16722
21. Sim MR. The COVID-19 pandemic: major risks to healthcare and other workers on the front line. Occup Environ Med 2020; 77: 281-2.
22. European Society of Gynaecological Oncology (ESMO). ESMO Management and treatment adapted recommendations in the COVID-19 era: endometrial cancer. 2020. Available at: https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic/gynaecological-malignancies-endometrial-cancer-in-the-covid-19-era
23. European Society of Gynaecological Oncology (ESMO). ESMO Management and treatment adapted recommendations in the COVID-19 era: cervical cancer. 2020. Available at: https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic/gynaecological-malignancies-cervical-cancer-in-the-covid-19-era
24. Spanish Society of Gynecology and Obstetrics. Recommendations of the gynecological oncology and breast disease section of SEGO on management of gynecological tumors during the COVID-19 pandemic. 2020. Available at: https://www.esgo.org/media/2020/03/Recommendations-of-the-Gynecological-Oncology-and-Breast-Disease-Section-of-SEGO-on-management-of-gynecological-tumors-during-the-COVID-19-pandemic.pdf
25. Royal College of Obstetricians and Gynaecologists (RCOG). Joint RCOG, BSGE and BGCS guidance for the management of abnormal uterine bleeding in the evolving coronavirus (COVID-19) pandemic. 2020. Available at: https://www.bgcs.org.uk/wp-content/uploads/2020/03/Joint-RCOG-BSGE-BGCS-guidance-for-management-of-abnormal-uterine-bleeding-AUB-in-the-evolving-Coronavirus-COVID-19-pandemic.pdf
26. American College of Surgeons. COVID-19 guidelines for triage of cancer surgery patients. 2020. Available at: https://www.facs.org/covid-19/clinical-guidance/elective-case/cancer-surgery
27. The American Society for Reproductive Medicine (ASRM). Joint statement on elective surgeries. 2020. Available at: https://www.asrm.org/news-and-publications/covid-19/statements/joint-statement-on-elective-surgeries/
28. Karimi-Zarchi M, Mousavi AS, Dehghani A. Conservative surgery in cervical cancer: report of two radical abdominal trachelectomies and literature review. Eur J Gynaecol Oncol 2011; 32: 710-2.
29. Karimi-Zarchi M, Dehghani-Firoozabadi R, Tabatabaie A, Dehghani-Firoozabadi Z, Teimoori S, Chiti Z, et al. A comparison of the effect of levonorgestrel IUD with oral medroxyprogesterone acetate on abnormal uterine bleeding with simple endometrial hyperplasia and fertility preservation. Clin Exp Obstet Gynecol 2013; 40: 421-4.

Safety and efficacy of synchronous panniculectomy and endometrial cancer surgery in obese patients: a systematic review of the literature and meta-analysis of postoperative complications

Anastasia Prodromidou[1], Christos Iavazzo[1], Victoria Psomiadou[1], Athanasios Douligeris[1], Nikolaos Machairas[2], Anna Paspala[2], Konstantinos Bakogiannis[1], George Vorgias[1]

[1]Department of Obstetrics and Gynecology, Metaxa Memorial Cancer Hospital, Piraeus, Greece

[2]Department of Surgery, Attikon University Hospital, National and Kapodistrian University of Athens School of Medicine, Athens, Greece

Abstract

Panniculectomy combined with gynaecological surgery constitutes an alternative approach for endometrial cancer (EC) in obese patients. The present study aimed to assess the current knowledge concerning the safety and efficacy of combining panniculectomy in surgical management of EC. Four electronic databases were systematically searched for articles published up to May 2019. A total of five studies, of which two were non-comparative and three comparative, were included. Meta-analysis of complications among panniculectomy and conventional laparotomy group revealed no difference in either intra- or post-operative complication rates. Moreover, no difference was reported in surgical site complications (p=0.59), while wound breakdown rates were significantly elevated in the laparotomy group (p=0.02). Panniculectomy combined surgery for the management of EC appears to be a safe procedure and results in comparable outcomes compared with conventional laparotomy with regard to complications and improved wound breakdown rates. (J Turk Ger Gynecol Assoc 2020; 21: 279-86)

Keywords: Panniculectomy, endometrial cancer, obesity, lymphadenectomy, wound complications

Received: 03 June, 2019 **Accepted:** 02 December, 2019

Introduction

Endometrial cancer (EC) remains the most common gynaecological cancer in the United States (1,2). In 2018, approximately 63,230 new cases of EC were diagnosed, with over 11,350 cancer-related deaths, while the relevant proportions from Global Cancer Statistics were 382,069 and 89,929, respectively (1,3). Moreover, obesity rates have escalated rapidly during the last decade and a continued steady increase is predicted, at least until 2030. Obese patients represent a particular patient population and thus require special management (4). Additionally, a significant correlation between obesity and the development of various malignancies including pancreatic, liver, and breast cancer and EC has been described (5).

Obesity is not only a risk factor for EC but also an important technical obstacle for its surgical management. Panniculectomy is a frequently performed procedure by plastic surgeons for the repair of abdominal wall malformations induced by massive weight loss (6). Compared to other aesthetic procedures, it has been associated with an increased risk of post-operative complications. These include wound-related complications, such as hematoma, seroma, wound infection and cellulitis or general complications such as venous thromboembolism (6). Recent studies reported a significant improvement in the incidence of complications after abdominoplasty due to improvement in operative techniques and perioperative

Address for Correspondence: *Anastasia Prodromidou*
e.mail: a.prodromidou@hotmail.com ORCID: orcid.org/0000-0002-4250-1853

Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2019.2019.0103

care (7). Panniculectomy combined with gynaecological surgery has been reported as a different approach to the peritoneal cavity and has gained wide acceptance, since it provides a more favourable surgical field and the associated complications can be well managed (8).

The aim of the present review was to combine and assess the current knowledge concerning the safety and efficacy of combining panniculectomy with gynaecological surgery in the management of patients with EC and to compare the outcomes with those of conventional surgery for EC.

Material and Methods

Study design

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed for the design of the present systematic review and meta-analysis. The search was based on the authors' predetermined eligibility criteria (9). An independent search of the literature was performed by three authors (C.I., A.P., V.P.) who excluded overlaps and tabulated the selected indices in a structured form. No language restrictions were assigned. Prospective and retrospective studies, which were either comparative or non-comparative and addressed outcomes of women with EC who underwent surgical staging with concomitant panniculectomy were considered eligible for inclusion in the present systematic review. Reviews, case reports, abstracts and animal studies were excluded from analysis and tabulation.

Search strategy and data collection

A systematic search of the literature was conducted for articles published up to May 2019. Databases searched were PubMed (1966-2019), Google Scholar (2004-2019), Scopus (2004-2019), and the ClinicalTrails.gov database, along with the references of the articles retrieved in full text. The key words which were used for the search were: "EC", "uterine cancer", "corpus cancer", "panniculectomy", "apronectomy", "lymphadenectomy". A limited number of keywords were used with the intent to assess an eligible number, which could be easily searched and, at the same time, minimizing the potential loss of eligible articles. Articles that fulfilled or were considered to fulfil the eligibility criteria were retrieved in full text. All studies with more than 10 cases of obese women with EC, aged >18 years, who underwent a combination of surgical management for EC with panniculectomy, were included. Comparative and non-comparative studies reporting at least one postoperative outcome including operative time (OT), estimated blood loss (EBL), length of hospital stay (LOS), resected lymph nodes count (pelvic or para-aortic) and incidence of complications, were considered eligible for inclusion. Comparative studies which presented outcomes of obese patients who had surgery for EC with additional panniclulectomy versus those who had did not undergo panniculectomy and received only conventional EC-related surgical procedures were also considered eligible for inclusion. The meta-analysis was based on the assessment of the complication rates as the primary outcome. The stages of selection of the recruited articles are schematically presented in Figure 1 which depicts the PRISMA flow diagram.

Quality assessment

The Methodological Index for Non-Randomized Studies (MINORS) was utilized to assess the quality of the recruited studies (10). MINORS consists of a quality assessment tool which was designed to estimate non-randomized studies methodological adequacy. Due to the fact that all the studies included in the present meta-analysis were non-randomized, the MINORS scale was used.

Statistical analysis

The RevMan 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011) was used for

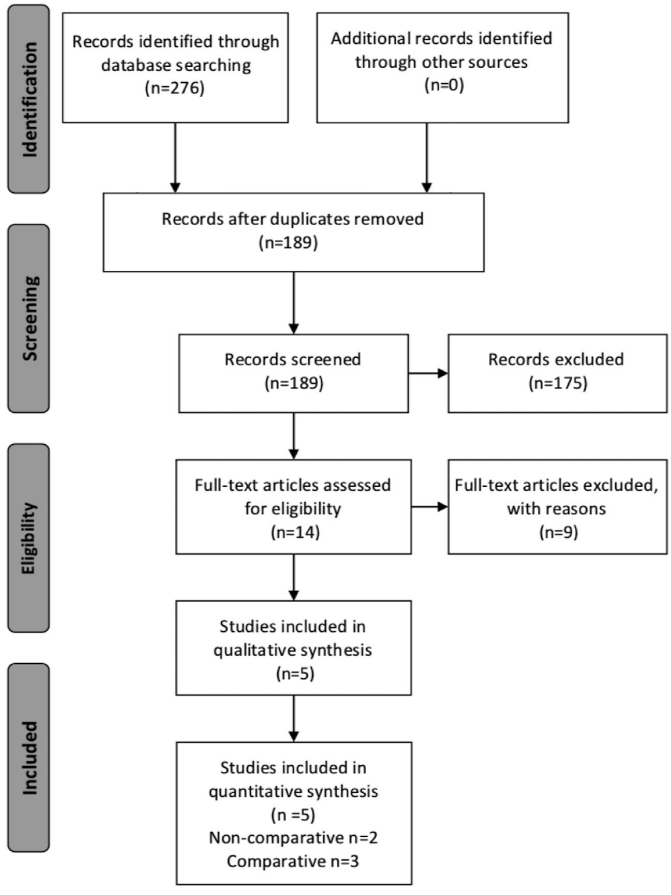


Figure 1. Search flow diagram

statistical meta-analysis. Confidence intervals (CI) were set at 95%, whereas mean difference and odds ratios (OR) were used for the analysis. In all the examined parameters, the DerSimonian-Laird random effect model was utilized, due to the expected significant heterogeneity of the studies (11). P-value <0.05 was set as the cut-off for statistical significance. Due to the fact that heterogeneity of the included studies may influence the methodological integrity of the tests, publication bias was not tested.

Results

Due to the high heterogeneity of the included studies and more specifically the discrepancy with regards to the way of interpretation of the examined parameters in comparative studies, meta-analysis of the results was precluded for most of the parameters. A meta-analysis was specifically performed for overall and surgical site complications. Therefore, for the remaining parameters a meticulous systematic review was conducted. The analysed indices were tabulated in three structured tables as follows: Table 1, included the main characteristics of comparative and non-comparative studies; Table 2, 3 recorded the main characteristics of the patients and the main intra- and post-operative outcomes, respectively.

Excluded studies

A total of nine studies were excluded from this systematic review. More specifically, six reported outcomes with regards to gynecologic oncology surgical procedures combined with panniculectomy were initially considered eligible. After retrieving the full text, it was noticed that no separated outcomes for patients operated for EC were provided and the studies was excluded (12-17). Additionally, Cosin et al. (18) and Micha et al. (19) were not included, due to limited patient numbers. Finally, in the study by Patibandla et al. (20) insufficient data made it ineligible for inclusion.

Included studies

Five studies, which reported patients who underwent surgery for EC with or without panniculectomy were finally included in the present study (21-25). Specifically, two studies were non-comparative and included 33 patients (21,22) while the remaining three studies were comparative studies and evaluated results of 65 patients who received simultaneous laparotomy for EC and panniculectomy (Panniculectomy group) versus 416 who underwent laparotomy only for EC (Laparotomy group) (23-25).

Quality assessment

The MINORS quality assessment revealed methodological adequacy of the included studies and the presence of low heterogeneity with regards to their quality. A mean score of 13.8 (standard deviation: 4.5) with a respective median score of 16 (range: 8-18) (Table 1) were calculated.

Table 1. Characteristics of included studies

Author; year	Type of study	Quality assessment	Inclusion criteria	Procedure performed
Non-comparative studies (laparotomy + panniculectomy)				
Crosbie et al. (21), 2011	RS	10/16	Panniculectomy at the time of laparotomy staging and tumour debulking	AH and salpingo-oophorectomy
Powell et al. (22), 1999	RS	8/16	Panniculectomy at the time of gynecologic surgical procedures	Radical or simple hysterectomy
Comparative studies (laparotomy + panniculectomy vs laparotomy)				
Ramzan et al. (23), 2015	RS	17/24	Hysterectomy-based surgical staging; no sarcoma, endometrial hyperplasia, and metastatic cancer to the endometrium	AH based surgical staging (type 1 or type 2-3 or supracervical hysterectomy)
Eisenhauer et al. (25), 2007	RS	16/24	Surgical staging for endometrial cancer; patients with BMI ≥35 kg/m^2	Peritoneal washing, AH and bilateral salpingo-oophorectomy in intact ovaries, pelvic and/or para-aortic lymphadenectomy
Wright et al. (24), 2004	RS matched	18/24	N/A	AH and bilateral salpingo-oopherectomy in intact ovaries, pelvic and para-aortic lymphadenectomy

RS: Retrospective, AH: Abdominal hysterectomy, BMI: Body mass index, N/A: Not applicable

Intraoperative and postoperative outcomes

A total of 98 patients underwent surgery for EC and simultaneous panniculectomy. Seventy-seven women had stage I/II EC and nine had stage III/IV EC, according to FIGO classification, while for the remaining 12 patients staging was not reported (Table 2). Data of perioperative outcomes with regards to patients who underwent combined surgery, showed a median (range) OT of 247.7 (90-355) minutes and a median (range) EBL of 486.5 (50-1200) mL. The incidence of intraoperative complications was 8.5% (n=5/59). Median (range) LOS was 6 (3-15) days. Concerning postoperative complications, a total of 25 patients (25.5%) presented with non-surgical site complications, whereas 26 patients (26.5%) had surgical site complications. Among them, 13 were wound infections, six had cellulitis, and three wound breakdowns were reported while for the remainder data concerning the type of complication was not available (Table 3).

With regards to the comparative studies, as shown in Table 3, no difference in mean body mass index (BMI) among patients who underwent combined surgery and those who underwent only laparotomy was reported by the study of Wright et al. (24) whereas Ramzan et al. (23) and Eisenhauer et al. (25) reported significantly higher BMI in the panniculectomy group. Intraoperative outcomes revealed a significantly prolonged OT in the panniculectomy group in comparison to laparotomy group in all of the included studies ($p<0.001$) whereas EBL was not significantly different ($p>0.05$). No difference was reported with regards to LOS ($p>0.05$). Data from two of the studies showed that pelvic lymph node dissection was performed in 85.2% of patients in the panniculectomy group and in 57.2% in the laparotomy group (24,25). Eisenhauer et al. (25) reported a significantly elevated count of harvested pelvic lymph nodes in patients in the panniculectomy group ($p=0.001$). In contrast, Wright et al. (24) did not find a difference in mean pelvic lymph node count between the two groups ($p=0.199$). A total of 61% of patients from the panniculectomy group and 44% from the laparotomy group had para-aortic lymphadenectomy (24,25). Wright et al. (24) noted a significantly higher proportion of para-aortic lymph nodes dissected in the panniculectomy group when compared to women who underwent simple laparotomy ($p=0.032$). On the contrary, median para-aortic lymph node count did not differ among the two group of patients as reported by Eisenhauer et al. (25) ($p=0.18$).

Meta-analysis of complications revealed no difference in overall complication rates, when surgical site complications were excluded, among the two groups either in intra-operative or post-operative complications (481 cases, OR: 1.06 95% CI: 0.31-3.58 $p=0.93$ and 300 cases OR: 1.49 95% CI: 0.46-4.82 $p=0.51$, respectively). Concerning surgical site complications, the overall effect did not reveal a significant difference between the Panniculectomy and Laparotomy groups (481 cases OR: 0.74 95% CI: 0.25-2.21 $p=0.59$) (Figure 2). When incision related parameters, such as wound infection, cellulitis and wound breakdown were separately analyzed, statistical significance was noted only in wound breakdown rates, which were found to be significantly elevated in patients who did not undergo panniculectomy (262 cases OR: 0.14 95% CI: 0.03-0.75 $p=0.02$) (Figure 3). The incidence of wound infection and cellulitis did not differ between the two groups (262 cases OR: 0.53 95% CI: 0.11-2.44 $p=0.41$ and 262 cases OR: 0.93 95% CI: 0.05-16.20 $p=0.96$, respectively).

Table 2. Characteristics of included patients

Author; year	Patient no	Age (years)	BMI (kg/m^2)	Stage	Grade
Non-comparative studies (laparotomy + panniculectomy)					
Crosbie et al. (21), 2011	21	58 (34-74)[a]	49 (37-64)[a]	0:2, I:15, IIa:2, IIIc:2	N/A: 2, 1:10, 2:6, 3:3
Powell et al. (22), 1999	12	51 (38-65)[a]	51 (35-76)[a]	N/A	N/A
Comparative studies (laparotomy + panniculectomy vs laparotomy)					
Ramzan et al. (23), 2015	11 vs 208	48.0±11.7[b] vs 55.6±11.4[b]	60.4±11.9[b] vs 35.7±10.8[b] p<0.001	I:10 vs 128, II:0 vs 14, III:1 vs 31, IV:0 vs 35	1:10 vs 99 2:1 vs 39 3:0 vs 70
Eisenhauer et al. (25), 2007	27 vs 154	56 (37-78)[a] vs 60 (25-84)[a]	49 (35-64)[a] vs 41 (35-84)a p<0.001	I-II: 26 vs 142, III-IV: 1 vs 12	1:13 vs 91 2:8 vs 31 3:6 vs 32
Wright et al. (24), 2004)	27 vs 54	54,8[c] vs 56,2[c]	49.8 (27-84)[a] vs 44.1 (30-69)[a] p>0.05	I:18 vs 40, II:4 vs 8, III:4 vs 5, IV:1 vs 1	1:17 vs 30 2:5 vs 15 3:5 vs 9

[a]Median (range), [b]Mean ± standard deviation, [c]Mean, BMI: Body mass index, N/A: Not applicable

Discussion

The main aim of this systematic review was to evaluate the efficacy and safety of panniculectomy in selected cases who underwent surgery for EC by assessing the main peri-operative outcomes reported by the recruited studies. In patients undergoing combined surgery, the median OT in the laparotomy without panniculectomy group was 206.7 minimum and median EBL was 486.5 mL, while there was a similar prevalence of approximately 26% observed in non-surgical site and surgical site complications among the included patients. Despite the prolonged OT in the panniculectomy group, EBL and LOS were comparable among patients who had panniculectomy combined surgery and conventional EC surgery. Additionally, meta-analysis revealed no difference in either non-surgical site or in surgical site complications, whereas subgroup analysis of wound infection, cellulitis and wound breakdown revealed a difference only in the incidence of the latter.

Obese patients who undergo surgery for EC are potentially at higher risk of intra- or post-operative complications due to excess subcutaneous fat. To that end, application of panniculectomy has gained popularity as an additional procedure during surgery for the treatment of gynaecological malignancies, and more specifically, EC. Panniculectomy is a particular type of abdominoplasty, and tends to be less radical than other methods of abdominoplasty. It was initially applied in multiparous women who presented with a prominent apron in their abdominal wall (26). Favourable cosmetic and medical outcomes have also been reported in obese patients or patients that lost weight and suffer from an excess abdominal skin (26,27). The procedure involves removal of as much excess adipose tissue as can be resected without leaving tension of the remaining tissue at closure. The rectus muscle and its sheath, which is usually morbid in patients with large pannus, is then reconstructed (28). Umbilicus preservation is attempted. Specifically, a scalpel is usually used for transverse skin incisions and an electrosurgical source is used for the excision of the underlying subcutaneous tissue. The procedure is performed before entering the peritoneal cavity, entry to which is made through a midline incision. At the end of the procedure, the abdominal flaps are closed with sutures to the subcutaneous tissue, drainage is placed and the skin is also sutured.

In the present study, about one fourth of patients who underwent gynecological surgery combined with panniculectomy presented with either non-surgical site or surgical site post-operative complications. Despite the fact that this rate could be considered relatively high, there are in agreement to those reported by other studies, which examined the efficacy of panniculectomy combined surgery in obese patients with gynecological malignancies (29,30). More specifically, a retrospective study by Rasmussen et al. (29) evaluated post-operative complications after panniculectomy combined with

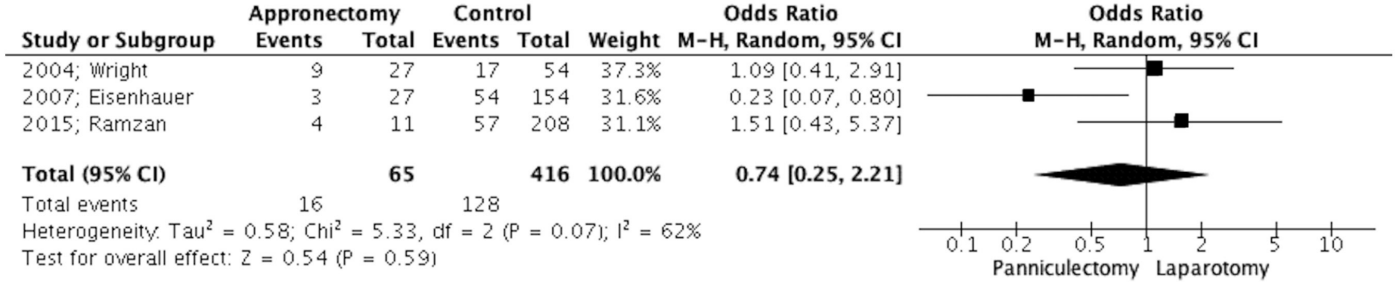


Figure 2. Forest plot depicting surgical site complication
CI: Confidence interval

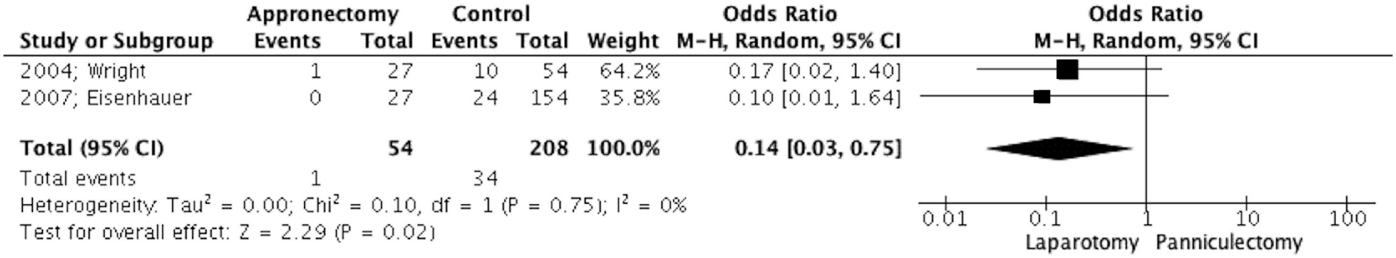


Figure 3. Forest plot depicting wound breakdown rates
CI: Confidence interval

Table 3. Main intra-and postoperative outcomes

Author; year;	Operative time (minimum)	Blood loss (mL)	Hospital stay (days)	No of resected Pelvic LN	No of paraaortic LN
Non-comparative studies (laparotomy + panniculectomy)					
Crosbie et al. (21), 2011	192 (148-240)[c]	497 (200-1000)[c]	9 (8-12)[a]	N/A	N/A
Powell et al. (22), 1999	166 120-225	500 (100-1200)	7 (3-10)	N/A	N/A
Comparative studies (laparotomy + panniculectomy vs laparotomy)					
Ramzan et al. (23), 2015	395±133 vs 260±103 p<0.001	436±301 vs 486±548 p=1.0	4 (3-11) vs 4 (2-41) p=1.0	N/A	N/A
Eisenhauer et al. (25), 2007	265 (171-355) vs 164 (40-368) p<0.001	250 (50-700) vs 200 (40-2200) p=0.07	6 (4-15) vs 6 (4-56) NS	22 (5-45)/19 vs 12 (1-34)/69 p=0.001	5 (2-8)/9 vs 4 (1-12)/49 p=0.18
Wright et al. (24), 2004)	247.7 vs 206.7 p=0.001	486.5 vs 417.6 p=0.180	6 vs 5.3 p=0.417	16.2 vs 13.6 p=0.199	4.3 vs 2.9 p=0.032

*No surgical site complications, LN: Lymph node, [a]Median (range), [b]Mean±SD, [c]Mean (range), N/A: Not applicable

a gynecologic procedure, such as hysterectomy (simple or radical) or laparotomy for ovarian cancer staging. The overall complication rates were 31.3% and most were superficial cellulitis (28.3%) (29). Furthermore, according to a comparative study by Forte et al. (30) no significant differences were detected with regards to overall and wound-related complications among patients who underwent panniculectomy combined hysterectomy and those who had hysterectomy alone. Similarly, the present meta-analysis revealed no difference in wound infection rates and cellulitis among the patients included. On the contrary, the authors suggested that the significantly increased wound breakdown rates in the simple laparotomy group are possibly due to the excessive pannus that remained after surgery in this group.

Lymph node yield could be considered as a quantitative method of evaluation of the efficacy of panniculectomy, which results in an improvement in the vision of the surgical field during surgical management of EC. In that setting, a potential increase in the count of resected lymph nodes could indicate the superiority of panniculectomy combined surgery for EC (20). Eisenhauer et al. (25) reported the resected lymph node count was significantly increased in patients who also had panniculectomy compared to those who underwent simple laparotomy. However, no difference was detected among the two groups by Wright et al. (24). However, data is still limited and further studies are warranted to resolve this question.

Considering that panniculectomy is a relatively rare procedure for non-cosmetic indications, combined with simultaneous advances in minimally invasive procedures in the management of EC, there may be increasing confusion concerning the exact indications for this procedure. Nonetheless, in case of obese and extremely obese patients, minimally invasive surgery still remains challenging, because of the technical difficulties that are related to excess fat and the impact on the visualization, the radicallity of the procedure and the OTs (31). Panniculectomy combined procedures could be considered as an alternative for patients with high BMI. Outcomes from the included studies imply a good safety profile for the procedure, despite the fact that they derive from small retrospective studies. Additionally, the precise indications of the procedure, the BMI above which patients could benefit from the procedure, along with the extent of pannus are not properly identified. To that end, Ramzan et al. (23) suggested that patients with BMI of more than 60 kg/m^2 as well as patients who will require lymph node dissection could be considered as candidates for panniculectomy. However, further randomized controlled trials, which evaluate the outcomes after minimally invasive surgery, simple laparotomy and panniculectomy-combined laparotomy are needed, in order to identify the most appropriate approach according to each BMI and designate the candidates for panniculectomy.

Study Limitation

There are some limitations that need to be addressed. First of all, the retrospective nature of the articles included, along with their heterogeneity, constitute significant limitations. Furthermore, all the studies included were non-randomized which further limits the interpretation of the exact role of patients' characteristics as confounders. Concerning the comparative studies, the control groups were not matched with regards to patient characteristics. Consequently, the

Surgical site complications (n, %)	Intraoperative complication* (n, %)	Postoperative complications* (n, %)	Wound infection (n, %)	Cellulitis (n, %)	Wound breakdown (n, %)	Mortality (n, %)
7/21	0/21	5/21	4/21	2/21	1/21	0/11
3/12	N/A	3/12	0/12	0/12	1/12	0/12
4/11 vs 57/208	0/11 vs 15/208	4/11 vs 34/208	N/A	N/A	N/A	0/11 vs 1/208
3/27 vs 54/154	N/A	5/27 vs 61/154	3/27 vs 48/154	3/27 vs 45/154	0/27 vs 24/154	N/A
9/27 vs 17/54	5/27 vs 6/54	8/27 vs 13/54	6/27 vs 4/54	1/27 vs 0/54	1/27 vs 10/54	1/27 vs 0/54

panniculectomy group included patients with significantly greater BMI compared to control in two of the recruited studies, is an additional limitation of our findings. Furthermore, the definition of obesity was not consistent between the included studies. Therefore, potential bias with regards to selection and attrition bias and selective reporting may skew our outcomes. In some studies, report of the outcomes measures was inadequate, especially with regards to continuous parameters such as lymph node yield, in which outcome reports different methods were utilized for the interpretation of the results and thus some were not included in the analysis. Accordingly, oncological outcomes were underreported by the included studies. More specifically, disease free survival and overall survival rates were only available in the study by Wright et al. (24) who reported comparable rates among the two groups. Furthermore, the small sample sizes of the included patients in each group constituted a further limitation of our study. Finally, assessment of publication bias was not feasible concerning the small size of the studies included.

Conclusion

Panniculectomy combined surgery for the management of EC can be considered a safe procedure in selected patients and presents with comparable outcomes to conventional laparotomy procedures with regard to non-surgical and surgical site complications and improved wound breakdown rates. However, those outcomes must be cautiously interpreted because of the limited number of studies included in this meta-analysis and their retrospective nature. To the best of our knowledge, the present study is the only one in this field which assessed post-operative results in patients who had panniculectomy combined surgery for EC in obese patients. There is a need for further, larger-volume studies with the intention of defining the optimal approach, specifying the group of obese patients with EC who could benefit from panniculectomy and elucidate the efficacy of panniculectomy in enhancing the lymph node yield in those patients.

Peer-review: *Externally peer-reviewed.*

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

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

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018; 68: 7-30.
2. Prodromidou A, Vorgias G, Bakogiannis K, Kalinoglou N, Iavazzo C. MELF pattern of myometrial invasion and role in possible endometrial cancer diagnostic pathway: a systematic review of the literature. Eur J Obstet Gynecol Reprod Biol 2018; 230: 147-52.
3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394-424.
4. Hagemann AR, McCourt CK, Varaday SS, Moore KN. Defining and mitigating the challenges of an older and obese population in minimally invasive gynecologic cancer surgery. Gynecol Oncol 2018; 148: 601-8.

5. Hubbard VS. Defining overweight and obesity: what are the issues? Am J Clin Nutr 2000; 72: 1067-8.
6. Winocour J, Gupta V, Ramirez JR, Shack RB, Grotting JC, Higdon KK. Abdominoplasty: risk factors, complication rates, and safety of combined procedures. Plast Reconstr Surg 2015; 136: 597e-606e.
7. Dutot MC, Serror K, Al Ameri O, Chaouat M, Mimoun M, Boccara D. Improving safety after abdominoplasty: a retrospective review of 1128 cases. Plast Reconstr Surg 2018; 142: 355-62.
8. Pearl ML, Valea FA, Disilvestro PA, Chalas E. Panniculectomy in morbidly obese gynecologic oncology patients. Int J Surg Investig 2000; 2: 59-64.
9. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009; 339: b2700.
10. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg 2003; 73: 712-6.
11. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. Contemp Clin Trials 2007; 28: 105-14.
12. Wallace SA, Mericli AF, Taylor PT, Drake DB. Panniculectomy and abdominoplasty in patients undergoing gynecologic surgery: a single center case series of 15 combined procedures. Ann Plast Surg 2013; 71: 88-92.
13. Blomfield PI, Le T, Allen DG, Planner RS. Panniculectomy: a useful technique for the obese patient undergoing gynecological surgery. Gynecol Oncol 1998; 70: 80-6.
14. Hopkins MP, Shriner AM, Parker MG, Scott L. Panniculectomy at the time of gynecologic surgery in morbidly obese patients. Am J Obstet Gynecol 2000; 182: 1502-5.
15. Pearl ML, Valea FA, Chalas E. Panniculectomy and supraumbilical vertical midline incisions in morbidly obese gynecologic oncology patients-a prospective, controlled trial of low-dose heparin. J Am Coll Surg 1998; 6: 649-53.
16. Wright JD, Rosenbush EJ, Powell MA, Rader JS, Mutch DG, Gao F, et al. Long-term outcome of women who undergo panniculectomy at the time of gynecologic surgery. Gynecol Oncol 2006; 102: 86-91.
17. Tillmanns TD, Kamelle SA, Abudayyeh I, McMeekin SD, Gold MA, Korkos TG, et al. Panniculectomy with simultaneous gynecologic oncology surgery. Gynecol Oncol 2001; 83: 518-22.
18. Cosin JA, Powell JL, Donovan JT, Stueber K. The safety and efficacy of extensive abdominal panniculectomy at the time of pelvic surgery. Gynecol Oncol 1994; 55: 36-40.
19. Micha JP, Rettenmaier MA, Francis L, Willenberg R, Brown JV. "Medically necessary" panniculectomy to facilitate gynecologic cancer surgery in morbidly obese patients. Gynecol Oncol 1998; 69: 237-42.
20. Patibandla JR, Kufel CN, Hopkins MP. Evaluation of extended antibiotic prophylaxis in patients undergoing indicated non-cosmetic panniculectomy at the time of gynecologic surgery. J Surg Oncol 2018; 117: 1337-41.
21. Crosbie EJ, Estabragh ZR, Murphy J, Ahmed AS, Slade RJ. Apronectomy combined with laparotomy for morbidly obese endometrial cancer patients. Surg Oncol 2011; 20: e187-93.
22. Powell JL, Kasparek DK, Connor GP. Panniculectomy to facilitate gynecologic surgery in morbidly obese women. Obstet Gynecol 1999; 94: 528-31.
23. Ramzan AA, Garcia-Sayre J, Hom MS, Graham KA, Carey JN, Muderspach LI, et al. Relative morbidity and mortality of panniculectomy-combined surgical staging in endometrial cancer. Int J Gynecol Cancer 2015; 25: 1503-12.
24. Wright JD, Powell MA, Herzog TJ, Mutch DG, Rader JS, Gao F, et al. Panniculectomy: improving lymph node yield in morbidly obese patients with endometrial neoplasms. Gynecol Oncol 2004; 94: 436-41.
25. Eisenhauer EL, Wypych KA, Mehrara BJ, Lawson C, Chi DS, Barakat RR, et al. Comparing surgical outcomes in obese women undergoing laparotomy, laparoscopy, or laparotomy with panniculectomy for the staging of uterine malignancy. Ann Surg Oncol 2007; 14: 2384-91.
26. Pestana IA, Campbell D, Fearmonti RM, Bond JE, Erdmann D. "Supersize" panniculectomy: indications, technique, and results. Ann Plast Surg 2014; 73: 416-21.
27. Umeadi UP, Ahmed AS, Murphy J, Slade RJ. Apronectomy in combination with major gynaecological procedures. J Obstet Gynaecol 2008; 28: 516-8.
28. Michaels J, Coon D, Calotta NA, Peter Rubin J. Surgical management of the giant pannus: indications, strategies, and outcomes. Aesthetic Plast Surg 2018; 42: 369-75.
29. Rasmussen RW, Patibandla JR, Hopkins MP. Evaluation of indicated non-cosmetic panniculectomy at time of gynecologic surgery. Int J Gynaecol Obstet 2017; 138: 207-11.
30. Forte AJ, Tuggle CT, Berlin NL, Fischer JP, Persing JA. Hysterectomy with concurrent panniculectomy: a propensity-matched analysis of 30-day outcomes. Plast Reconstr Surg 2015; 136: 582-90.
31. Menderes G, Gysler SM, Vadivelu N, Silasi DA. Challenges of robotic gynecologic surgery in morbidly obese patients and how to optimize success. Curr Pain Headache Rep 2019; 23: 51.

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

Postoperative pain management in obstetrics and gynecology

Henning Ohnesorge[1], Veronika Günther[2], Matthias Grünewald[1], Nicolai Maass[2], İbrahim Alkatout[2]

[1]Clinic of Anesthesiology and Operative Intensive Medicine, University Medical Center Schleswig-Holstein, Kiel, Germany

[2]Clinic of Obstetrics and Gynecology, University Medical Center Schleswig-Holstein, Kiel, Germany

Abstract

The efficiency and quality of postoperative pain management may be considered unsatisfactory in Europe, as well as in the United States. Notwithstanding our better understanding of the physiology of pain and the development of new analgesia procedures, the improvement in satisfaction of patients has not be enhanced to the same degree. Obstetrics and gynecology are no exception to this statement. In fact, obstetrics and gynecology are surgical departments in which patients experience the greatest severity of postoperative pain. Current concepts of postoperative pain management are largely based on the administration of systemic non-opioid and opioid analgesics, supplemented with regional analgesia procedures and/or peripheral nerve blockades and, in some cases, the administration of other pain-relieving pharmaceutical agents. Based on the existing body of evidence, it would be appropriate to develop procedure-related concepts of analgesia. The concepts are based on the special circumstances of the respective department, and the scheme of analgesia is aligned to the respective interventions. Generally, however, a surgeon's individual experience in dealing with the procedures and substances could be more significant than the theoretical advantages demonstrated in preceding investigations. (J Turk Ger Gynecol Assoc 2020; 21: 287-97)

Keywords: Pain management, obstetrics, gynecology, nerve block, anesthesia

Received: 27 February, 2020 **Accepted:** 15 May, 2020

Introduction

Despite significant progress in our comprehension of the mechanisms of pain, pain physiology, and the pharmacology of effective analgesic substances, postoperative pain management remains a major challenge in medicine. Insufficiently treated postoperative pain impairs postoperative convalescence in many ways and thus also influences perioperative morbidity and the duration of hospital stays. Despite the advancements made in some areas with regard to the treatment of postoperative pain, the quality of postoperative pain management is generally unsatisfactory in Europe, as well as in the United States (1-3). This does not necessarily mean that major operations are associated with very intense pain and minor procedures involve less pain. Rather, it has been noted in patient surveys that analgesia is rather poor after routine and frequently performed operations, whereas - contrary to general expectations - major operations are rated positively by patients (4). One of the reasons for this discrepancy could be the patients' expectations. Those who undergo major operations tend to anticipate and accept pain.

Postoperative pain management needs to be improved to a large extent in obstetrics and gynecology as well. This is reflected by the fact that the pain scores of patients in Departments of Obstetrics and Gynecology, German Hospitals are higher than those at all other surgical departments (5). Gynecological operations are also reported to cause high levels of pain. Especially open operations in the uterus are associated with severe pain; the latter is comparable with pain scores after spondylodesis. Thus, open operations in the uterus are followed by the highest pain scores in Germany. However, complex operations in the female breast and supposedly minor laparoscopic interventions such as adenectomies are also associated with significant postoperative pain (6). In fact, pain

Address for Correspondence: *Ibrahim Alkatout*
e.mail: ibrahim.alkatout@uksh.de ORCID: orcid.org/0000-0002-7194-6034

Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.

DOI: 10.4274/jtgga.galenos.2020.2020.0024

scores in the afore-mentioned settings exceed those reported after major operations in the upper abdomen (such as partial resection of the liver) (5).

Current concepts of postoperative pain therapy are usually based on a combination of various analgesics and/or regional anesthesia to achieve a balanced analgesia regimen and adequate pain relief while causing acceptable side effects.

Aims of postoperative pain management

The foremost aim of pain management is not to alleviate the intensity of pain but to reduce the patient's suffering. The principle that applies here is: "Suffering may be associated with the significance of pain to the same extent as it is with the intensity of pain. A persistent feeling of helplessness and hopelessness may be the basic cause of a patient's suffering when he/she experiences chronic pain. This is reflected in high pain scores" (7). Extrapolated to the postoperative situation, this means that the patient's satisfaction and well-being should be given greater attention (8). In an investigations of patients who had undergone a caesarean section alone, questions focusing on the patient's well-being rather than pain were able to influence their feedback concerning postoperative pain and their desire to receive more analgesics (9).

Factors other than the severity of pain were also found to influence a patient's postoperative well-being. Especially the occurrence of nausea and vomiting are significant factors. The possibility of independent mobilization, particularly going to the toilet and personal hygiene, having sufficient sleep at night, being able to dispense with drainages, catheters and intravenous accesses, and a largely normal oral intake of food are important in this context. In summary, in the postoperative phase patients wish to achieve sufficient control over their physical symptoms as well as restore their autonomy rapidly. Interestingly, the wishes of patients are very similar to the postoperative goals of the Enhanced Recovery after Surgery (ERAS) Programme (10).

Despite these long-term goals, the severity of postoperative pain must be recorded regularly. This is usually achieved with the aid of a numeric rating scale (NRS) extending from 0 (no pain) to 10 (worst pain). However, the use of the NRS requires a certain capacity for abstraction on the part of the patient. Basically, postoperative pain should be recorded regularly and after any type of pain therapy in order to evaluate the success of the respective measure.

Systemic analgesics

Non-opioid analgesics

Non-opioid analgesics constitute the basis of analgesia in postoperative pain management. The regular administration of individual non-opioids, such as paracetamol, traditional non-steroidal anti-inflammatory drugs (NSAIDs), selective cyclooxygenase-2 (COX-2) inhibitors or metamizole in standard doses provides sufficient pain relief after interventions associated with mild or moderate pain (11). The analgesic potency of non-opioid analgesics after oral administration has been extensively investigated (12) (Figure 1). We lack similar investigations for intravenous forms of application. In patients undergoing operations that involve severe pain, the regular administration of non-opioid analgesics as part of a balanced concept of analgesia may contribute to a reduction of opioid doses as well as side effects, and improve the quality of analgesia.

Paracetamol

Of all non-opioid analgesics, paracetamol is regarded as the substance with the least analgesic potency (Figure 1). The analgesic efficacy of intravenous administration is more pronounced than that of oral or rectal administration. Paracetamol is well tolerated in therapeutic doses and has no relevant cardiovascular, gastrointestinal, or renal side effects. It also has no clinically significant impact on the function of thrombocytes. However, the use of paracetamol is controversially discussed because of its limited therapeutic spectrum and the risk of irreversible liver damage in case of overdosage. The highest daily dose for oral or rectal administration is 100 mg/kg body weight, and for intravenous administration 4 g/24 h (for those with a body weight less than 50 kg the dose is 60 mg/kg BW). Previous damage to the liver, a glutathione deficiency, such as that caused by excessive alcohol consumption, or the induction of the CYP-450 enzyme system, are listed as contraindications for the use of paracetamol.

Metamizole

In addition to its favorable pain-relieving effect, metamizole has spasmolytic effects which may intensify its analgesic effect,

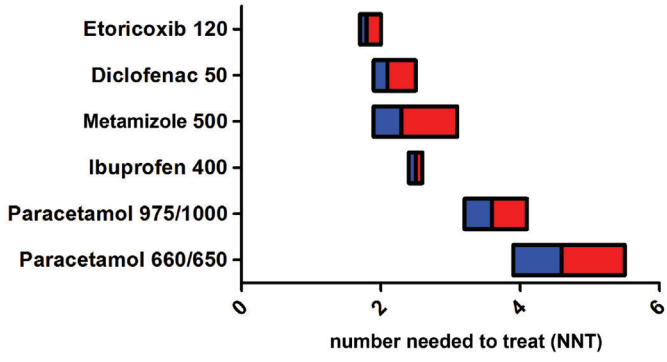


Figure 1. Analgesic potency of various non-opioid analgesics: Number needed to treat in order to reduce pain by at least 50% in patients with moderate to severe pain (red/blue: 95% confidence interval, median, based on (12)

especially in cases of colic or convulsive pain. However, in view of the fact that metamizole could trigger agranulocytosis, its use in Germany is restricted to five indications:

1. Acute and severe pain after injuries and/or operations,
2. Colic,
3. Tumor pain,
4. Any other acute or chronic severe pain, provided other therapeutic measures are not indicated,
5. High fever that does not respond to other measures.

These indications do not necessarily include the postoperative use of metamizole after operations. Rather, they refer to its use in the event of anticipated or existing severe postoperative pain. Owing to the risk of shock reactions, the parenteral administration of metamizole is explicitly indicated only when oral administration is not feasible (13).

Although the incidence of metamizole-induced agranulocytosis is considered to be rather low compared to that of other pharmacological agents, explaining the risks of using metamizole to the patent prior to its intended use has become an avidly discussed issue again. Agranulocytosis may also occur after prolonged treatment with metamizole and after a period of several days following its last administration. Therefore, it would be meaningful to inform the patient after the administration of metamizole about potential early symptoms of metamizole-induced agranulocytosis (fever, throat pain, inflammatory changes in the mucous membranes).

Notwithstanding these limitations, metamizole remains an essential component of the concept of balanced postoperative pain management because of its high tolerability and low or non-existent organ toxicity. Therefore, metamizole still is the preferred non-opioid analgesic for postoperative pain management in German-speaking countries (14).

Non-steroidal antiphlogistic drugs

Traditional non-selective COX inhibitors as well as selective COX-2 inhibitors are marked by their significant analgesic effect in postoperative pain management. However, the use of traditional NSAIDs and coxibs is limited because of their spectrum of side effects. These especially include cardiovascular, renal, and gastrointestinal effects. Basically, the risk of gastrointestinal events is markedly higher during the long-term intake of nearly all NSAIDs and coxibs (15). The latter rule out the use of NSAIDs or coxibs in nearly all patients with relevant cardiovascular risk factors (CHD, heart failure NYHA II-IV, peripheral arterial occlusive disease, cerebrovascular disease). The same considerations apply to the risk of gastrointestinal bleeding. Substances with a gastrointestinal risk profile are associated with a higher risk of cardiovascular events as well.

As these substances have an effect on renal function, their postoperative use is contraindicated, especially in patients with a pre-existing limitation of renal function or hypovolemia. The latter can never be ruled out after major operations.

Furthermore, when using non-specific NSAIDs, one must take into account the fact that the inhibition of COX-1 may lead to a disorder of thrombocyte function. Thus, these substances may be associated with a higher risk of hemorrhage after surgery. In a recent meta-analysis, however, no elevated incidence of hematoma or post-surgical hemorrhage was registered after plastic operations (including those in the breast) and the intake of NSAIDs (16).

Opioid analgesics

In patients with severe postoperative pain that cannot be adequately controlled with non-opioid analgesics, opioids still are the gold standard in postoperative pain management. In Germany piritramide has been established as a standard medication, although we lack robust evidence of the superiority of this substance over other opioids such as morphine, fentanyl or sufentanil. Intravenous administration is advantageous in the short term because of its rapid efficacy and the easy titration of these substances.

Opioids are marked by their favorable analgesic effect and the absence of organ toxicity. However, the spectrum of acute side effects of opioids in the postoperative phase is of considerable relevance. The administration and dosage of opioids for postoperative pain management is one of the major risk factors for the occurrence of nausea and vomiting. Furthermore, the inhibition of bowel motility, which occurs frequently under opioid treatment, is responsible for the delayed postoperative restoration of normal gastrointestinal function. The deleterious effects of opioids on respiratory depression in case of overdosage are a matter of great concern (17). The highly variable need for opioids in patients and the absence of predictive tools to address this problem are further difficulties (4). Thus, the administration of opioids in the postoperative phase is usually titrated according to the individual patient's needs.

Opioids are titrated by the nursing staff and the substance is usually given in the form of short intravenous infusions, but these may be associated with the risk of relative overdosage. Therefore, if a patient needs opioids regularly, it would be advisable to use patient-controlled application systems patient-controlled analgesia (PCA). As the latter is administered frequently in smaller individual doses, this form of analgesia is associated with a lower risk of overdosage (Figure 2). Simultaneously, the use of PCA systems improves the quality of postoperative pain management (18).

The disadvantage of traditional PCA systems that permit intravenous administration of an opioid through a pump system

is the indispensable need for an intravenous access and the consequent limitation of the patient's mobility. A new system that permits patient-controlled administration of sufentanil sublingual microtablets is an alternative that, according to preliminary data, provides at least equivalent pain relief as intravenous PCA; it causes no limitation of the patient's mobility and provides a greater degree of satisfaction for patients (19).

The perioperative use of retarded opioids is a further alternative to the purely need-oriented administration of opioids. The notion of administering a fixed dose of a retarded opioid does contradict the observation that the postoperative requirement of opioids varies very markedly from one patient to another. Therefore, recent American guidelines for postoperative pain therapy explicitly advise against the use of long-acting opioids in the early postoperative phase (20). The summaries of product characteristics for retarded opioids also clearly mentions that the substances should not be administered preoperatively or during the first 12-24 hours post-surgery. Nevertheless, clinical experience concerning the long-term administration of retarded opioids and the need-oriented administration of a non-retarded oral opioid has been quite favorable (21) (Figure 3).

Gabapentinoids

In addition to traditional non-opioid and opioid analgesics, particularly gabapentin and pregabalin have been established in the management of postoperative pain. The preoperative administration of these substances, which are approved for the treatment of chronic neuropathic pain, appears to reduce the need for opioids as well as the incidence of nausea and vomiting after breast surgery and open hysterectomy (22,23). The effective dose remains unclear. The use of higher doses is quite evidently associated with a sedative effect.

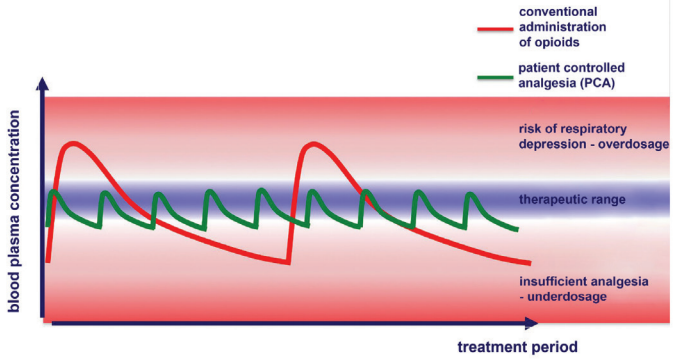


Figure 2. Theoretical course of plasma levels after conventional administration of opioids by nursing staff (infrequent application, higher doses) compared to patient-controlled application (PCA, small dose, frequent administration)

Systemic local anesthetics

The perioperative systemic administration of lidocaine is, in part, propagated as the "poor man's epidural" because initial studies have shown a marked effect on the postoperative need for analgesics, the duration of gastrointestinal atony, and the incidence of opioid-related undesirable effects. In a recent Cochrane analysis (24), the effect of this procedure could not be clearly proven in comparison with placebo or traditional epidural analgesia. Therefore, the results of further studies are required before this procedure can be recommended as a standard for the management of perioperative pain.

Regional anesthesia procedures

For many operations in obstetrics and gynecology, regional anesthesia procedures can be used to reduce the patient's need for systemic analgesics and simultaneously improve the management of postoperative pain. The spectrum extends from wound infiltrations and peripheral nerve blockades to analgesia procedures in the vicinity of bone marrow, especially epidural and peridural analgesia.

Wound infiltration

Wound infiltrations can be performed as a single-shot procedure or a continuous procedure, usually through a subcutaneous catheter connected to an elastomeric pump. While wound infiltrations in patients undergoing general and traumatological surgery have shown marked effects, the data reported in the obstetric and gynecological setting have been disappointing. Wound infiltrations as a means of postoperative pain management are recommended neither in laparoscopic surgery of the lower abdomen nor in surgery on the female breast (25,26). After caesarean section, wound infiltrations may reduce the need for opioids without influencing the incidence of opioid-related undesirable effects (27).

Peripheral nerve blockade

Various types of peripheral nerve blockades may be used for postoperative pain management in obstetrics and gynecology. Paravertebral blockades (PVB) and pectoral nerve blockades (PECS I + II) in breast surgery, as well as the transversus abdominis plane (TAP) block in surgery of the lower abdomen are worthy of mention.

Paravertebral blockade

PVB are regarded as a unilateral alternative to epidural analgesia procedures and are mainly used in the chest. After injection of local anesthetics in the paravertebral space, the anesthetist administers analgesia that usually reaches several

segments and thus influences the roots of spinal nerves. PVB's have been successfully used for many years in breast surgery as a means of perioperative pain management (28). It should be noted that a PVB may also be used to reduce the occurrence of chronic pain after breast surgery in women (29). The risk of undesirable effects (nerve injury, pneumothorax, vessel puncture) is considered negligible (28). However, a disadvantage is that PVB must be administered preoperatively or postoperatively with the patient in sitting position and wide awake. This reduces the acceptance of the procedure.

Pectoral nerve block

The pectoral fascia block was first described in 2011 as an alternative to PVB (30). This was followed by various modifications of the procedure. Currently, a combination of fascia blocks between the pectoralis major and pectoralis minor muscles (PECS I block), and the pectoralis minor and serratus anterior muscles (PECS II block) at the level of the fourth rib has been established as a standard procedure. This combination appears to be as effective as a PVB (31). Its advantages are that it has a low risk profile even when administered after the induction of general anesthesia in a supine position (32).

Transversus abdominis plane block

TAP block is a field block, similar to PECS. It encompasses the abdominal wall branches of the thoracic spine and lumbar spine nerve roots, and is used as a means of perioperative analgesia, especially when performing surgery in the lower abdomen. A depot of a local anesthetic is injected into the layer of fascia between the internal oblique muscle and the transversus abdominis muscle, in the medioclavicular line between the costal arch and the iliac crest. In gynecology, operations performed through a laparotomy of the lower abdomen are a favorable indication for this procedure. However, these operations require a bilateral blockade. Rather high volumes (15-20 mL each) are needed to achieve adequate distribution of the anesthetic. In particular, when administering a bilateral blockade, the concentration of the local anesthetic must be adjusted to avoid overdosage (33).

Epidural analgesia

Regional anesthesia procedures used in the vicinity of bone marrow, especially epidural analgesia, are regarded as the gold standard in postoperative analgesia for several abdominal operations. However, the risk-benefit ratio beyond the obstetric setting is a critically debated issue. Therefore, indications for epidural analgesia as a means of perioperative pain management are on the wane (34).

This is because the advantages of epidural anesthesia, as compared to systemic analgesia procedures in combination with other less invasive regional anesthesia procedures (see above), was not very pronounced in recent studies, as in older ones. The reason for this development could be the more consistent use of "ERAS" concepts. Poor bowel preparation and the limitation of preoperative fasting, early enteral nutrition, the omission of drains, and consistent early mobilization of the patient appear to be more significant for the outcome of surgery than the elimination of sympathetic innervation, the opioid-saving effect, and improved analgesia through epidural anesthesia.

On the other hand, according to recent investigations, the risk of relevant undesirable effects of epidural analgesia outside the field of obstetrics, are higher than previously estimated. In an assessment of more than 1.3 million procedures performed in the USA, the risk of spinal hematoma after epidural analgesia procedures for abdominal surgery was reported to be 1:7500 (95% confidence interval: 1:5,663-1:9,736) (35). One of the major unmodifiable risk factors is the Charlson Comorbidity Index. In view of the potentially fatal consequences of epidural hematoma, a careful risk-benefit analysis should be performed, especially in multimorbid patients.

Currently, epidural procedures are no longer recommended as a means of perioperative pain therapy for laparoscopic operations. In multivisceral resection for ovarian cancer, depending on the individual risk profile of the patient, epidural analgesia procedures still constitute a standard approach. However, even for these operations, the positive impact of epidural analgesia on the severity of postoperative pain appears to be limited to the first three days post-surgery. Epidural analgesia was found to have no effect on morbidity, especially the duration of gastrointestinal atony or the incidence of other opioid-induced side effects (36).

The risk-benefit ratio of epidural analgesia procedures is still rated positively in obstetrics. On the one hand, the superiority of peripartum analgesia compared to systemic analgesia procedures is still undisputed. Due to the widespread absence of comorbidities and the highly regulated coagulation system, the risk of severe complications is lower than that in a general postoperative setting; for example, the risk of epidural hematomas is reported to be about 1:150,000 (35). Nevertheless, the suitability of epidural analgesia for postoperative pain management after caesarean section is limited because the injection is given at the level of the lumbar spine, and motor disabilities in the lower extremities cannot be ruled out.

Preemptive analgesia

Preemptive analgesia is any treatment given to the patient prior to surgery, in order to reduce or prevent subsequent pain. This specifically means that by initiating analgesia (and anaesthesia) prior to the initiation of noxious stimuli, peripheral, and central nervous system pain receptor activation is blocked. This leads to a reduced activity of pain neurotransmitters, processing can be modified, which results in improved short-term and long-term pain control and reduced side effects from narcotic analgesics (37).

Long et al. (38) analyzed a total of 324 studies concerning preemptive analgesia in minimally invasive gynecologic surgery (MIGS). Preemptive blocks, like paracervical, triple antibiotic paste, or pudendal block appear to have the most consistently beneficial effect on postoperative pain in MIGS with an excellent cost-benefit ratio. Preemptive anticonvulsants, ketamine and dexmedetomidine have a positive effect on postoperative pain and opioid use but are limited by side effects. Preemptive dexamethasone, acetaminophen, and NSAIDs have a modest effect on postoperative pain control (38).

Another study group from the US analyzed the effectiveness of preemptive analgesia for pain control in women undergoing total abdominal hysterectomy (39). Sixty-nine randomized controlled trials were included. Concerning nonnarcotic medications, paracetamol, gabapentin, and rofecoxib combined with gabapentin led to improvements in pain assessment compared with placebo and other nonnarcotic medications. The use of preemptive paracetamol, gabapentin, bupivacaine, and phenothiazine resulted in less narcotic usage than placebo (39).

Fast-track surgery (FTS) programs - also known as ERAS - have the aim of ERAS, allowing earlier discharge with improved patient outcomes. Such programs derive their success from their multidisciplinarity, including surgeons, nurses, anesthetists, pain specialists, ward nursing staff, social workers, occupational and physical therapy staff (40). Concerning the anesthesiologic side, the following subjects should be considered: preoperative sedative premedication should be avoided in order to allow early patient mobilization, initiation of early oral feeding and catheter removal (41).

The method of action concerning preemptive analgesia was described earlier in the last section. For preemptive local anaesthesia, a TAP block can be performed just after intubation and just before surgery is commenced. For preemptive analgesia, the administration of Gabapentin can be used. A large number of randomized controlled trials have confirmed decreased analgesic requirements after preoperative gabapentin (42,43).

Further preemptive analgesia is initiated with COX-2 inhibitors given intravenously pre- and intra-operatively (parecoxib) with intravenous paracetamol (44). In addition, intravenous (and oral) paracetamol has opioid sparing effects (45).

Early mobilization and early oral feeding are both central components for a successful FTS.

Both can be better managed through good postoperative pain management. The mobilization is associated with an increased blood circulation and helps to reduce the risk of venous thrombo-embolism. Furthermore, improved pulmonary function with an expansion of the lung bases and better tissue oxygenation should be noted (37).

Special features of postoperative pain management during puerperium and lactation

Postoperative pain management in the postpartum period is challenging because the patient has a significant need for analgesia, especially after a caesarean section, and the analgesic agents are associated with a risk of toxic effects on the colostrum and breast milk, with potentially harmful effects on the breast-fed infant. At least in German-speaking countries, the need for analgesia in this period is underestimated while the risks for the newborn are overestimated. This miscalculation does not restrict the use of analgesic treatment on the part of the treating physicians alone. Patients also tolerate a high level of pain before they ask for analgesics that, in their estimation, may potentially affect breast milk. This is because of their (unwarranted) concern regarding toxic effects on the newborn. Sufficient analgesia is especially important during the puerperium, because it is a prerequisite for early mobilization of the patient and the avoidance of postpartum thrombosis, and is also a predictor of the success of breastfeeding. Last but not least, one must consider the fact that the risk and severity of puerperal depression are linked with the severity of postpartum pain. These ideas mentioned before, form a contrast to pain management in oncological gynecology. In many cases, oncological patients have become accustomed to their pain over a long period of time and often take analgesics as permanent medication - sometimes in increasing doses due to increasing pain or an incipient habituation effect. This is in contrast to obstetric patients who experience a new form of pain from complete health.

Blood-milk barrier

The blood-milk barrier has similar properties as the placental barrier and hinders the entry of pharmaceutical agents into breast milk to a limited extent. In many cases, small molecules and lipophilic substances can be freely transferred to breast milk. The pH-dependent load of the substances is

of crucial importance (Figure 4). Acidic substances, such as ibuprofen, are virtually absent from breast milk, whereas alkaline substances, such as opioids, accumulate in breast milk. In addition to the milk/plasma ratio, which describes the extent of transfer of a pharmaceutical agent into breast milk, the quantity of breast milk ingested by the newborn infant is also a significant determinant of the neonatal dose. While infants ingest breast milk at a rate of about 150 mL/kg body weight, the quantity of colostrum is much less during the first few days postpartum. Consequently, even if the mother is given high doses of opioids during the puerperium, the load on the newborn infant is negligible. For instance, even after mothers were given high doses of oxycodone during the first 48 hours postpartum, only one of 41 breast-fed infants had detectable and clinically relevant oxycodone levels in plasma (46).

Regrettably, we lack robust data for many pharmaceutical agents and their use in the postpartum period and during lactation. The largest body of clinical experience is available for paracetamol (M/P coefficient 1), ibuprofen (M/P coefficient 0.008) and fentanyl, which is widely used in English-speaking countries. However, due to similar pharmacodynamics and pharmacokinetics, this experience is also applicable to other opioids such as tramadol, piritramide or oxycodone (M/P coefficient 2-3.6). Codeine and pethidine are exceptions. Their use should be avoided during pregnancy and lactation because of their cumulative metabolic effects. The establishment of a maximal dose of opioids during the postpartum period is not meaningful because neither maternal plasma levels nor levels of the substances in breast milk are correlated with the doses of opioids (46).

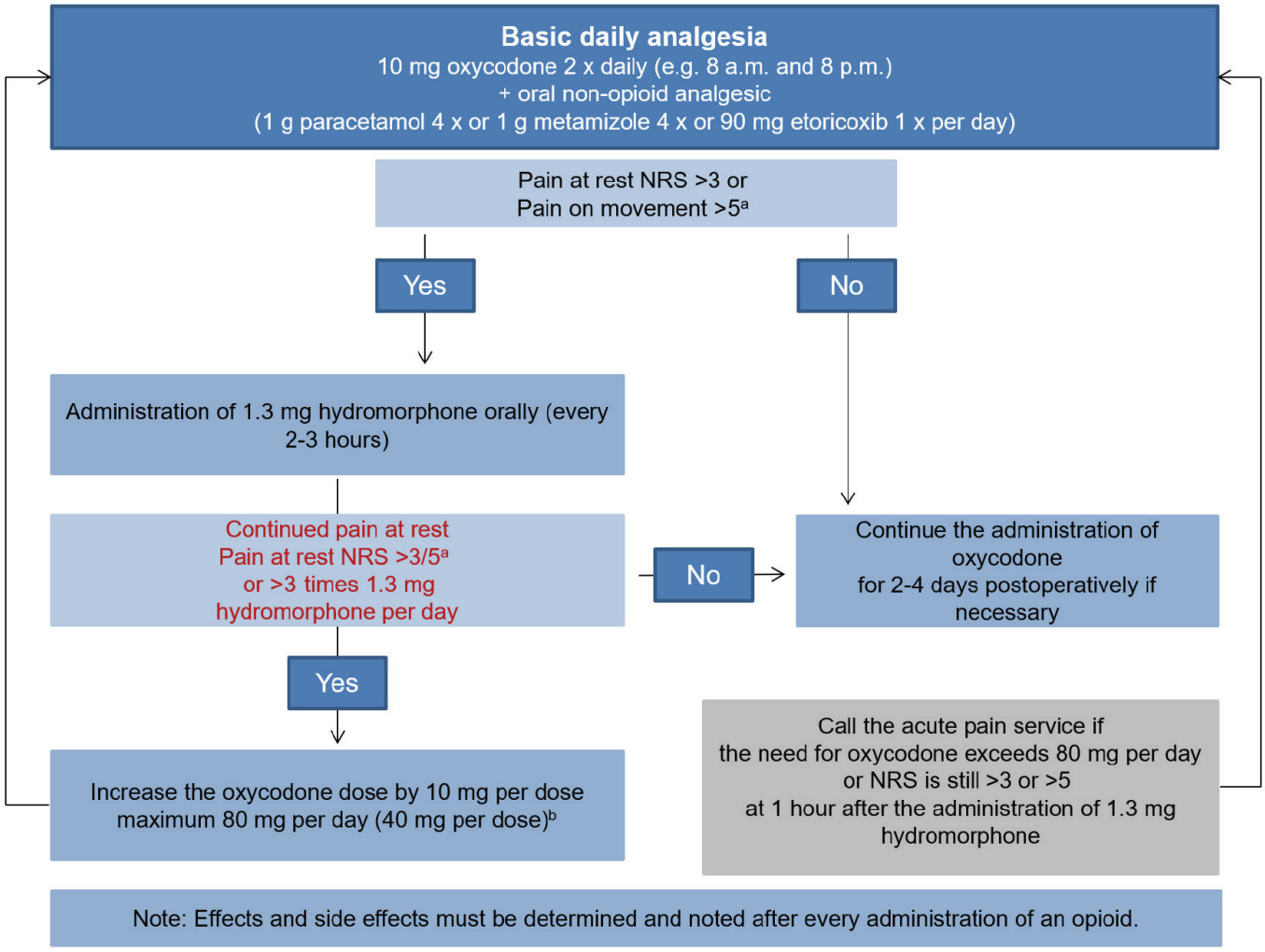


Figure 3. Concept of postoperative pain management: basic treatment with non-opioid analgesics and retarded opioids, and need-oriented treatment with non-retarded oral opioids [extracted from (47)], "numeric rating scale".
[a]The reason for existing or increasing postoperative pain should be investigated by the surgeon in charge of the patient's treatment. [b]The success or failure of any change in basic analgesia must be determined.
NRS: Numeric rating scale

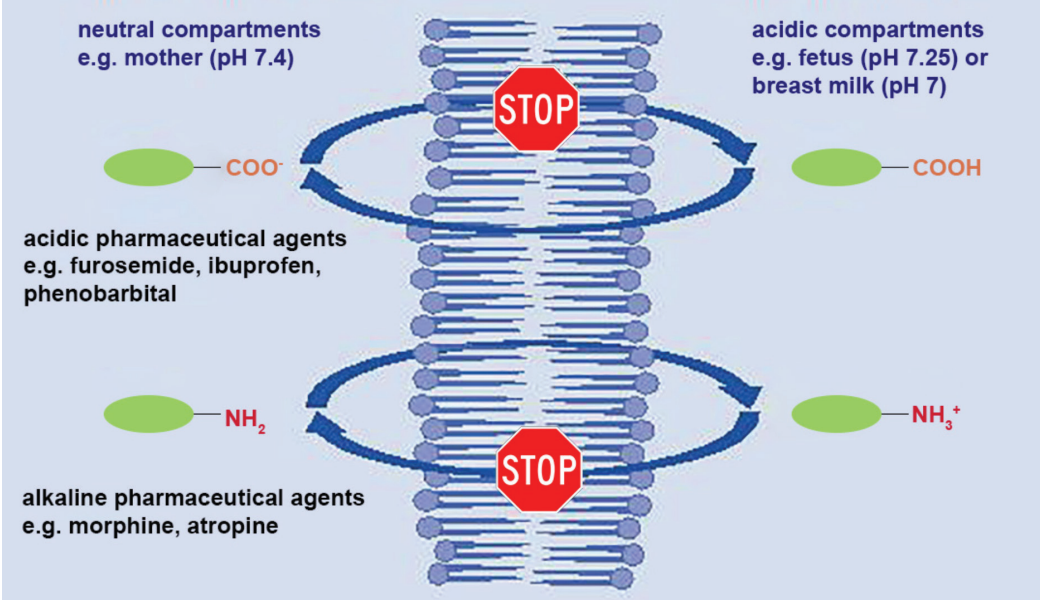


Figure 4. Ion trap. Acids absorb a hydrogen ion in an acidic environment and are not charged with it (= lipophilic = can pass through membranes). In a neutral or alkaline environment, they release a hydrogen ion and are charged with it (= hydrophilic = cannot pass through membranes). Therefore, they accumulate in an alkaline or neutral environment. Alkaline pharmaceutical agents behave in the opposite manner and accumulate in acidic compartments such as the fetus or breast milk [extracted from (48)]

Procedure-specific pain management in obstetrics and gynecology

The surgical spectrum of obstetrics and gynecology is wide. No general concept of postoperative pain management can be recommended for these specialties. Rather, it would be meaningful to develop procedure-specific concepts of postoperative pain management in cooperation with the involved clinical departments (obstetrics and gynecology, anesthesia, nursing staff, and pediatrics if applicable). We have evidence-based recommendations of the European Society of Regional Anaesthesia and Pain Therapy for some operations. However, some of these are outdated. In view of the above mentioned therapy options, one alternative for procedure-specific pain management in obstetrics and gynecology is listed in Table 1. When aligning these therapy

Table 1. Concept of procedure-specific postoperative pain management in obstetrics and gynecology. The use of treatment concepts must be aligned to the individual patient's risk profile

Procedure	Systemic analgesia	Regional anesthesia
Minor vaginal operations e.g. curettage, hysteroscopy	**Postoperatively;** Ibuprofen 400-600 mg orally if required. In case of contraindication to NSAIDs: Paracetamol 1 g orally if needed Tramadol 50-100 mg orally if needed	None
Major vaginal operations e.g. vaginal hysterectomy, plastic surgery	**Intraoperatively;** Metamizole 1 g iv. **Postoperatively;** Metamizole 4x1 g orally Piritramide 2-7.5 mg iv. if needed	None
Minor operations in the breast e.g. segment resection, sentinel lymph node biopsy	**Intraoperatively;** Paracetamol 1 g i.v. **Postoperatively;** Ibuprofen 3x400-600 mg orally. In case of contraindication to NSAIDs Paracetamol 4x1 g orally Piritramide 2-7.5 mg iv. if required	None

Table 1. Continued

Procedure	Systemic analgesia	Regional anesthesia
Major operations in the breast e.g. mastectomy, reconstructive procedures	(if necessary gabapentin 300-600 mg preoperatively (off-label) **Intraoperatively;** Paracetamol 1 g iv. **Postoperatively;** Ibuprofen 3x400-600 mg orally. In case of contraindication to NSAIDs Paracetamol 4x1 g orally Piritramide 2-7.5 mg iv. if required (if necessary gabapentin 300-600 mg preoperatively (off-label)	PVB or PECS I+II block
Minor laparoscopic procedures e.g. diagnostic laparoscopy, chromopertubation	**Intraoperatively;** Paracetamol 1 g iv. **Postoperatively:** Ibuprofen 3x400-600 mg orally. In case of contraindication to NSAIDs Paracetamol 4x1 g orally Piritramide 2-7.5 mg iv. if necessary	None
Major laparoscopic operations e.g. LASH, TLH, treatment of endometriosis	**Intraoperatively;** Metamizole 1 g iv. **Postoperatively;** Metamizole 4x1 g orally Piritramide 2-7.5 mg iv. if necessary (PCA system if necessary)	None
Open surgery in the lower abdomen e.g. open hysterectomy	(if necessary gabapentin 300-600 mg preoperatively (off-label) **Intraoperatively;** Metamizole 1 g iv. **Postoperatively;** Metamizole 4x1 g orally Piritramide 2-7.5 mg iv. if required (PCA system or retarded opioids if necessary (Figure 3)	Bilateral TAP block
Multivisceral resection e.g. in patients with ovarian cancer	**Intraoperatively;** Metamizole 1 g iv. **Postoperatively;** Metamizole 4x1 g iv. or orally Piritramide 2-7.5 mg iv. if required (PCA system if necessary)	Epidural analgesia
Caesarean section	**Postoperatively;** Ibuprofen 3x400-600 mg orally. In case of contraindication to NSAIDs Paracetamol 4x1 g orally Piritramide 2-7.5 mg iv. if required (or retarded opioids (Figure 3)	Wound infiltration, TAP block or spinal anesthesia with morphine (see textbooks on anesthesia)

NSAIDs: Non-steroidal anti-inflammatory drugs, PVB: Paravertebral blockades, PECS: Pectoral nerve blockades, PCA: Patient-controlled analgesia, TAP: Transversus abdominis plane, iv: Intravenous, LASH: Laparoscopic subtotal hysterectomy, TLH: Total laparoscopic hysterectomy

concepts to specific clinical conditions, one must consider the fact that the clinician's experience of the various procedures and pharmaceutical agents could be more important than the theoretical advantages reported in published studies.

Conclusion

The current non-optimum quality of postoperative pain therapy is not restricted to German-speaking countries alone. Furthermore, obstetrics and gynecology are not excepted from this statement. Rather, these surgical specialties are associated with the most severe postoperative pain.

Current concepts of postoperative pain management are largely based on the administration of systemic non-opioid and opioid analgesics. These are supplemented with regional anesthesia procedures, and in some cases with other pharmaceutical analgesics. Based on the existing body of evidence, it would be appropriate to develop procedure-specific analgesia

concepts that take the special characteristics of the specialties into account. In general, however, the clinician's personal experience of the procedures and substances could be more important than the theoretical advantages reported in published studies.

Peer-review: *Externally peer-reviewed.*

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

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

References

1. Rawal N. Current issues in postoperative pain management. Eur J Anaesthesiol 2016; 33: 160-71.
2. Wu CL, Raja SN. Treatment of acute postoperative pain. Lancet 2011; 377: 2215-25.
3. Argoff CE. Recent management advances in acute postoperative pain. Pain Pract 2014; 14: 477-87.
4. Wulf H. Postoperative schmerztherapie: wie geht's uns denn heute? AINS 2018; 53: 235-6.
5. Gerbershagen HJ, Aduckathil S, van Wijck AJ, Peelen LM, Kalkman CJ, Meissner W. Pain intensity on the first day after surgery: a prospective cohort study comparing 179 surgical procedures. Anesthesiology 2013; 118: 934-44.
6. Alkatout I, Mettler L, Maass N, Noe GK, Elessawy M. Abdominal anatomy in the context of port placement and trocars. J Turk Ger Gynecol Assoc 2015; 16: 241-51.
7. Ballantyne JC, Sullivan MD. Intensity of chronic pain--the wrong metric? N Engl J Med 2015; 373: 2098-9.
8. Mettler L, Ruprai R, Alkatout I. Impact of medical and surgical treatment of endometriosis on the cure of endometriosis and pain. Biomed Res Int 2014; 2014: 264653.
9. Chooi CS, White AM, Tan SG, Dowling K, Cyna AM. Pain vs comfort scores after caesarean section: a randomized trial. Br J Anaesth 2013; 110: 780-7.
10. Ljungqvist O, Scott M, Fearon KC. Enhanced recovery after surgery: a review. JAMA Surg 2017; 152: 292-8.
11. Jage J, Laufenberg-Feldmann R, Heid F. [Drugs for postoperative analgesia: routine and new aspects. Part 1: non-opioids]. Anaesthesist 2008; 57: 382-90.
12. Moore RA, Derry S, Aldington D, Wiffen PJ. Single dose oral analgesics for acute postoperative pain in adults - an overview of cochrane reviews. Cochrane Database Syst Rev 2015; 2015: CD008659.
13. Ärzteschaft ADD. Agranulozytose nach Metamizol - sehr selten, aber häufiger als gedacht (Aus der UAW-Datenbank). Dtsch Arztebl 2011; 108: 1758-9.
14. Reist L, Erlenwein J, Meissner W, Stammschulte T, Stüber F, Stamer UM. Dipyrone is the preferred nonopioid analgesic for the treatment of acute and chronic pain. A survey of clinical practice in German-speaking countries. Eur J Pain 2018; 22: 1103-12.
15. Bhala N, Emberson J, Merhi A, Abramson S, Arber N, Baron JA, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013; 382: 769-79.
16. Walker NJ, Jones VM, Kratky L, Chen H, Runyan CM. Hematoma risks of nonsteroidal anti-inflammatory drugs used in plastic surgery procedures: A Systematic Review and Meta-analysis. Ann Plast Surg 2019; 82(6S Suppl 5): S437-45.
17. Jage J, Laufenberg-Feldmann R, Heid F. [Drugs for postoperative analgesia: routine and new aspects: Part 2: opioids, ketamine and gabapentinoids]. Anaesthesist 2008; 57: 491-8.
18. McNicol ED, Ferguson MC, Hudcova J. Patient controlled opioid analgesia versus non-patient controlled opioid analgesia for postoperative pain. Cochrane Database Syst Rev 2015: Cd003348.
19. Melson TI, Boyer DL, Minkowitz HS, Turan A, Chiang YK, Evashenk MA, et al. Sufentanil sublingual tablet system vs. intravenous patient-controlled analgesia with morphine for postoperative pain control: a randomized, active-comparator trial. Pain Pract 2014; 14: 679-88.
20. Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T, et al. Management of postoperative pain: a clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain 2016; 17: 131-57.
21. Cheung CW, Ching Wong SS, Qiu Q, Wang X. Oral oxycodone for acute postoperative pain: a review of clinical trials. Pain Physician 2017; 20: SE33-52.
22. Rai AS, Khan JS, Dhaliwal J, Busse JW, Choi S, Devereaux PJ, et al. Preoperative pregabalin or gabapentin for acute and chronic postoperative pain among patients undergoing breast cancer surgery: a systematic review and meta-analysis of randomized controlled trials. J Plast Reconstr Aesthet Surg 2017; 70: 1317-28.
23. Li XD, Han C, Yu WL. Is gabapentin effective and safe in open hysterectomy? A PRISMA compliant meta-analysis of randomized controlled trials. J Clin Anesth 2017; 41: 76-83.
24. Weibel S, Jelting Y, Pace NL, Helf A, Eberhart LH, Hahnenkamp K, et al. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery in adults. Cochrane Database Syst Rev 2018; 6: CD009642.
25. Lirk P, Thiry J, Bonnet MP, Joshi GP, Bonnet F. Pain management after laparoscopic hysterectomy: systematic review of literature and prospect recommendations. Reg Anesth Pain Med 2019; 44: 425-36.
26. Cheng GS, Ilfeld BM. A review of postoperative analgesia for breast cancer surgery. Pain Manag 2016; 6: 603-18.
27. Bamigboye AA, Hofmeyr GJ. Local anaesthetic wound infiltration and abdominal nerves block during caesarean section for postoperative pain relief. Cochrane Database Syst Rev 2009: CD006954.
28. Schnabel A, Reichl SU, Kranke P, Pogatzki-Zahn EM, Zahn PK. Efficacy and safety of paravertebral blocks in breast surgery: a meta-analysis of randomized controlled trials. Br J Anaesth 2010; 105: 842-52.
29. Hussain N, Shastri U, McCartney CJL, Gilron I, Fillingim RB, Clarke H, et al. Should thoracic paravertebral blocks be used to prevent chronic postsurgical pain after breast cancer surgery? A systematic analysis of evidence in light of IMMPACT recommendations. Pain 2018; 159: 1955-71.
30. Blanco R, Fajardo M, Parras Maldonado T. Ultrasound description of pecs II (modified pecs I): a novel approach to breast surgery. Rev Esp Anestesiol Reanim 2012; 59: 470-5.
31. Kulhari S, Bharti N, Bala I, Arora S, Singh G. Efficacy of pectoral nerve block versus thoracic paravertebral block for postoperative analgesia after radical mastectomy: a randomized controlled trial. Br J Anaesth 2016; 117: 382-6.
32. Ueshima H, Otake H. Ultrasound-guided pectoral nerves (PECS) block: complications observed in 498 consecutive cases. J Clin Anesth 2017; 42: 46.

33. Griffiths JD, Barron FA, Grant S, Bjorksten AR, Hebbard P, Royse CF. Plasma ropivacaine concentrations after ultrasound-guided transversus abdominis plane block. Br J Anaesth 2010; 105: 853-6.
34. Bos EME, Hollmann MW, Lirk P. Safety and efficacy of epidural analgesia. Curr Opin Anaesthesiol 2017; 30: 736-42.
35. Rosero EB, Joshi GP. Nationwide incidence of serious complications of epidural analgesia in the United States. Acta Anaesthesiol Scand 2016; 60: 810-20.
36. Bardia A, Sood A, Mahmood F, Orhurhu V, Mueller A, Montealegre-Gallegos M, et al. Combined epidural-general anesthesia vs general anesthesia alone for elective abdominal aortic aneurysm repair. JAMA Surg 2016; 151: 1116-23.
37. Carter J. Fast-track surgery in gynaecology and gynaecologic oncology: a review of a rolling clinical audit. ISRN Surg 2012; 2012: 368014.
38. Long JB, Bevil K, Giles DL. Preemptive analgesia in minimally invasive gynecologic surgery. J Minim Invasive Gynecol 2019; 26: 198-218.
39. Steinberg AC, Schimpf MO, White AB, Mathews C, Ellington DR, Jeppson P, et al. Preemptive analgesia for postoperative hysterectomy pain control: systematic review and clinical practice guidelines. Am J Obstet Gynecol 2017; 217: 303-13.e6.
40. Carli F, Charlebois P, Baldini G, Cachero O, Stein B. An integrated multidisciplinary approach to implementation of a fast-track program for laparoscopic colorectal surgery. Can J Anaesth 2009; 56: 837-42.
41. Varadhan KK, Lobo DN, Ljungqvist O. Enhanced recovery after surgery: the future of improving surgical care. Crit Care Clin 2010; 26: 527-47, x.
42. Gilron I, Orr E, Tu D, O'Neill JP, Zamora JE, Bell AC. A placebo-controlled randomized clinical trial of perioperative administration of gabapentin, rofecoxib and their combination for spontaneous and movement-evoked pain after abdominal hysterectomy. Pain 2005; 113: 191-200.
43. Ajori L, Nazari L, Mazloomfard MM, Amiri Z. Effects of gabapentin on postoperative pain, nausea and vomiting after abdominal hysterectomy: a double blind randomized clinical trial. Arch Gynecol Obstet 2012; 285: 677-82.
44. Ong CK, Seymour RA, Lirk P, Merry AF. Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. Anesth Analg 2010; 110: 1170-9.
45. Maund E, McDaid C, Rice S, Wright K, Jenkins B, Woolacott N. Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs for the reduction in morphine-related side-effects after major surgery: a systematic review. Br J Anaesth 2011; 106: 292-7.
46. Seaton S, Reeves M, McLean S. Oxycodone as a component of multimodal analgesia for lactating mothers after caesarean section: relationships between maternal plasma, breast milk and neonatal plasma levels. Aust N Z J Obstet Gynaecol 2007; 47: 181-5.
47. Pogatzki-Zahn EM, Englbrecht JS, Pöpping D, Boche R, Zahn PK. [Oral therapy algorithm for the treatment of postoperative pain. A prospective observational study]. Schmerz 2013; 27: 26-37.
48. Böhm R, Ohnesorge H. Pharmakotherapie in der Schwangerschaft und Stillzeit. In: Kranke P, editor. Die geburtshilfliche Anästhesie. Berlin: Springer; 2018. p. 139-84.

What is your diagnosis?

An unmarried girl aged 17 years presented to our outpatient department with abdominal distension, dull aching abdominal pain, and amenorrhoea of three months duration. She attained menarche at 15 years of age and her previous menstrual cycles were regular, with average flow. General physical examination was within normal limit. Abdominal examination revealed a firm, non-tender, mobile abdomino-pelvic mass corresponding to 22 weeks of uterus size. Ultrasound (USG) showed a large solid cystic right adnexal mass with internal septations. In view of suspicion of ovarian malignancy, tumor markers were ordered. The serum values of CA-125 (28.5 U/mL), CA-19.9 (24.6 U/mL), carcinoembryonic antigen (0.67 ng/mL), alpha fetoprotein (1.5 IU/mL), and human chorionic gonadotropin (1.2 mIU/mL) were within normal limits and lactate dehydrogenase (LDH) (403 U/L) was raised. CECT abdomen and pelvis (Figure 1) suggested a well-defined, solid, multi-cystic abdomino-pelvic mass lesion (20.7x14.6x14 cm) arising from the right adnexa with enhanced septations and hyper dense component, which was thought to be probable ovarian adenocarcinoma. The right ovary was not evidently separate. The uterus was normal in size and the left ovary was not clearly visible. These findings led to a high clinical suspicion of ovarian malignancy and a plan of conservative staging laparotomy with right salpingo-ovariotomy was made in conjunction with the oncology department.

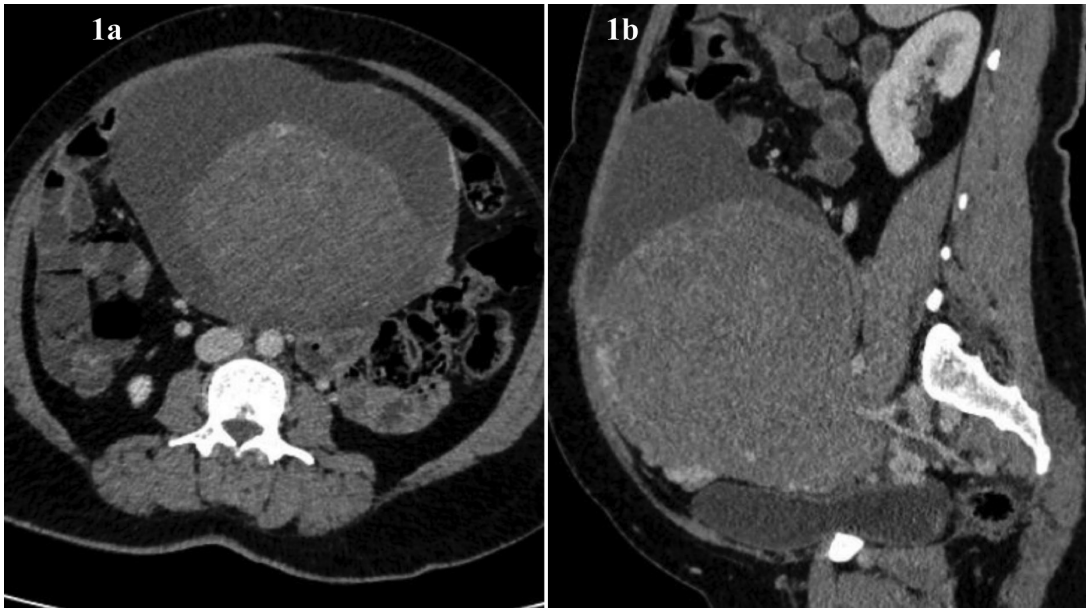


Figure 1. CECT abdomen & pelvis showing a well defined solid cystic lesion of size 20.7x14.6x14 cm arising from right adnexa with solid component measuring 18x14x14 cm (a) Transverse section, (b) Sagittal section

Received: 14 December, 2019 **Accepted:** 27 April, 2020

Address for Correspondence: *Kavita Khoiwal*
e.mail: kavita.kh27@gmail.com ORCID: orcid.org/0000-0002-3156-7486

Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2020.2019.0202

Answer

Laparotomy was performed and intraoperative findings were suggestive of bilateral ovarian masses, an 8x6 cm solid, cystic, left ovarian mass and a 10x8 cm multi-cystic, right ovarian mass (Figure 2). The left-sided mass appeared to be malignant with no salvageable ovarian tissue. Left salpingo-ovariotomy and right sided cyst drainage, followed by excision of cyst wall was performed. The cut section of the left ovarian mass showed both solid and cystic areas containing clear fluid, and a solid, white colored area (Figure 3). The right ovary had multiple, clear, fluid-filled cystic areas. Intraoperative frozen section was suggestive of serous cystadenoma. Her postoperative course was uneventful. Final histopathological examination (HPE) of the left ovary and right ovarian cyst wall revealed ovarian parenchyma with markedly loose and oedematous stroma, luteinisation of follicular cells, areas of hemorrhage and no atypia, suggestive of massive ovarian edema (MOE) (Figure 4).

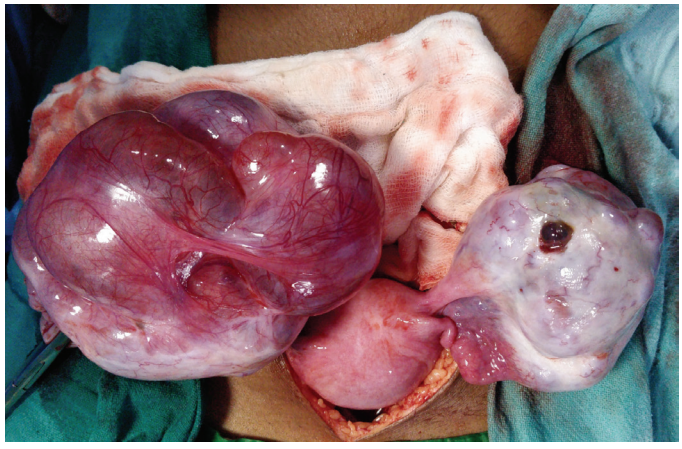


Figure 2. Intra-operative image suggestive of bilateral ovarian masses, an 8x6 cm solid cystic left ovarian mass and a 10x8 cm multi cystic right ovarian mass

MOE is defined by the World Health Organization as an accumulation of edema fluid in the stroma, separating normal follicular structures (1). It is a rare entity, first reported in 1969 by Kalstone et al. (2).

Most of the cases have occurred among reproductive age group women but have also been reported in a 6-month-old girl and in a post-menopausal woman (3,4). Almost 85% of these cases are unilateral and bilateral MOE is rarer (5). Patients usually present with abdominal pain in conjunction with palpable adnexal mass (6). Hormonal symptoms, such as menstrual irregularity, precocious puberty, infertility and virilization may be concurrent, due to stromal hyperplasia (5).

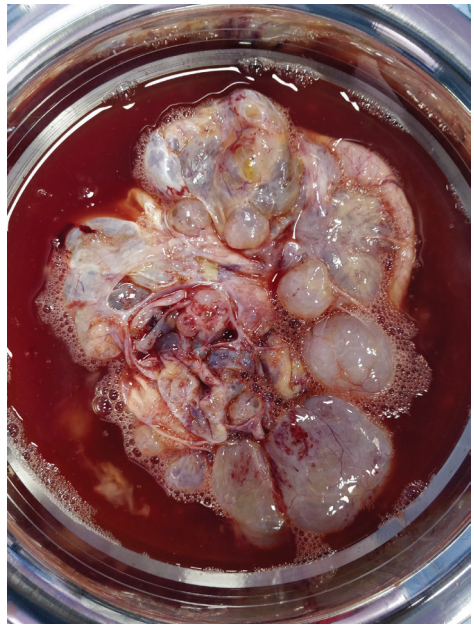


Figure 3. Cut specimen of left ovarian mass showing both solid and cystic areas containing clear fluid and a solid white-colored area

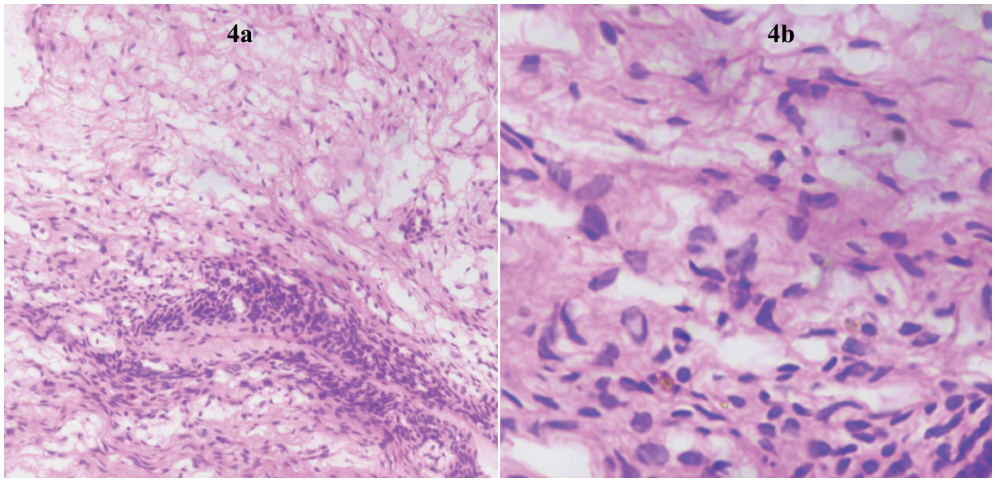


Figure 4. Hematoxylin and eosin (x10 and x40) stained section showing ovarian parenchyma with markedly loose and oedematous stroma, luteinisation of follicular cells, areas of hemorrhage and no atypia, suggestive of massive ovarian edema

The exact pathogenesis of MOE is still unknown but may be because of partial or complete ovarian torsion, secondary to PCOS, fibrothecoma, or metastatic carcinoma, all of which have been reported in the literature (2-4,7-9). When there is no underlying ovarian pathology, it is known as primary MOE. In the present case there was no evident underlying cause, and thus this is a case of primary MOE.

USG findings are inconclusive in most of the cases. Magnetic resonance imaging (MRI) has been found to be successful in diagnosing MOE, which shows an enlarged ovary with follicles around the ovary (10). In our case, the USG was inconclusive and CECT scan could not detect MOE. MRI was not requested as we did not suspect MOE. This is the rationale for publication of this case, as high clinical suspicion and awareness of the disease is crucial for optimal management.

Tumour markers are usually normal although raised LDH and CA-125 have been found in caes of ovarian edema with Meig's syndrome and fibrothecomas (8,9).

Although there may be a preoperative and intra-operative suspicion of MOE, the final diagnosis is made only on HPE. MOE usually mimics ovarian malignancy, which results in over-treatment with salpingo-ovariotomy. The mainstay of treatment is wedge resection of ovary (5). A high index of suspicion is crucial for correct diagnosis and to conserve fertility. Risk of recurrence and long term implications of MOE are yet to be studied.

MOE is a rare ovarian disorder mimicking ovarian malignancy. Most cases present in young girls and are over treated. Awareness of the disease and a high index of suspicion is the key to successful outcome.

Kavita Khoiwal[1], Payal Kumari[1], Om Kumari[1], Jaya Chaturvedi[1], Dr. Prashant Durgapal[2]

[1]Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, Rishikesh, India
[2]Department of Pathology, All India Institute of Medical Sciences, Rishikesh, India

References

1. Roth LM, Tsubara A, Dietel M, Senzaki H. Miscellaneous tumors and tumor-like con-ditions of the ovary. In: Tavassoli FA, Devilee P, editors. Pathology and Genetics of Tumors of the Breast and Female Genital Organs, World Health Organization Classifi-cation of Tumors. Lyon: IARC Press; 2003; 5: p.182-90.
2. Kalstone CE, Jaffe RB, Abell MR. Massive edema of the ovary simulating fibroma. Obstet Gynecol 1969; 34: 564-71.
3. Natarajan A, Wales JK, Marven SS, Wright NP. Precocious puberty secondary to mas-sive ovarian edema in a 6-month-old girl. Eur J Endocrinol 2004; 150: 119-23.
4. Shirk JO, Copas PR, Kattine AA. Massive ovarian edema in a menopausal woman. A case report. J Reprod Med 1996; 41: 359-62.
5. Houssein SG, Husslein H, Shore EM, Lefebvre G, Vlachou PA. bilateral massive ovarian edema due to chronic torsion treated with conservative laparoscopic approach. J Gynecol Surg 2018; 34: 327-30.
6. Praveen R, Pallavi V, Rajashekar K, Usha A, Umadevi K, Bafna U. A clinical update on massive ovarian oedema - a pseudotumour? E-Cancer Med Sci 2013; 7: 318.
7. Guvenal T, Cetin A, Tasyurt A. Unilateral massive ovarian edema in a woman with polycystic ovaries. Eur J Obstet Gynecol Reprod Biol 2001; 99: 129-30.
8. Lacson AG, Alrabeeah A, Gillis DA, Salisbury S, Grantmyre EB. Secondary massive ovarian edema with Meig's syndrome. Am J Clin Pathol 1989; 91: 597-603.
9. Sakaki M, Hirokawa M, Horiguchi H, Wakatsuki S, Sano T, Izumi Y. Ovarian fibroth-ecoma with massive edema. J Med Invest 2000; 47: 148-51.
10. Umesaki N, Tanaka T, Miyama M, Nishimura S, Kawamura N, Ogita S. Successful preoperative diagnosis of massive ovarian edema aided by comparative imaging study using magnetic resonance and ultrasound. Eur J Obstet Gynecol Reprod Biol 2000; 89: 97-9.

Unusual usage of the automated stapler in gynecologic oncology: method for diaphragmatic full thickness implant resection without entrance to pleural space

To the Editor,

The improved survival impact of achieving residue zero cytoreduction were proven in many studies for ovarian carcinoma (1,2). In those, one of the most commonly involved sites is the diaphragm in up to 40% of cases. Diaphragmatic involvement is one of the most common reasons for the failure to achieve complete or optimal cytoreduction surgery (3). Although there has been improvements in technique, experience, and education over the years, there are still concerns about complications and management of diaphragmatic tumor resection, especially in the presence of full thickness implants. Therefore, we would like to describe a technique for resection of diaphragm full thickness implants without entrance to the pleural space. Firstly, the liver was mobilized. Diaphragm striping was performed up to the full thickness implant. When an unresectable area was reached, the following technique was performed to resect the full thickness implant. The steps of the technique were: (i) after identification of the full thickness implant borderlines, sutures were placed to the medial, middle and lateral edges of the full thickness implant to more easily perform traction (Figure 1); (ii) an automated stapling device, such as thoraco-abdominal stapler DST series™ (Figure 2) or gastro-intestinal anastomosis stapler (DST series™) were placed transversally to diaphragm, under the full thickness implant which had been displaced by traction; (iii) in order to avoid lung parenchymal injury, the ventilator was temporarily turned off after exhalation, while the stapler was locked up; (iv) the stapler was locked up to place the sutures automatically; (v) the full thickness implant above the staplers was resected via manual scalpel for thoraco-abdominal stapler or by the integrated automated scalpel for gastro-intestinal anastomosis stapler, and the stapler was opened; (vi) the resection was completed without entrance to pleural space; and (vii) final control for air leakage using a bubble test, was performed. There were either no, or minimal, asymptomatic pleural

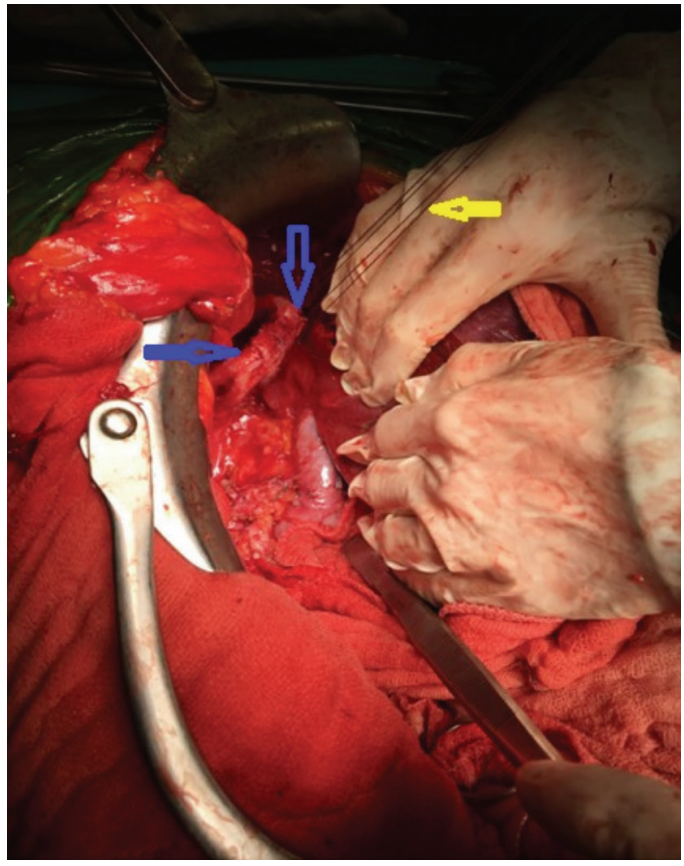


Figure 1. Sutures placed to the medial edge, the middle and the lateral edge of the full thickness implant to perform traction easier

Received: 06 February, 2020 **Accepted:** 16 June, 2020

Address for Correspondence: *Günsu Kimyon Cörnert*
e.mail: gunsukimyon@gmail.com ORCID: orcid.org/0000-0003-0178-4196

Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2020.2020.0008

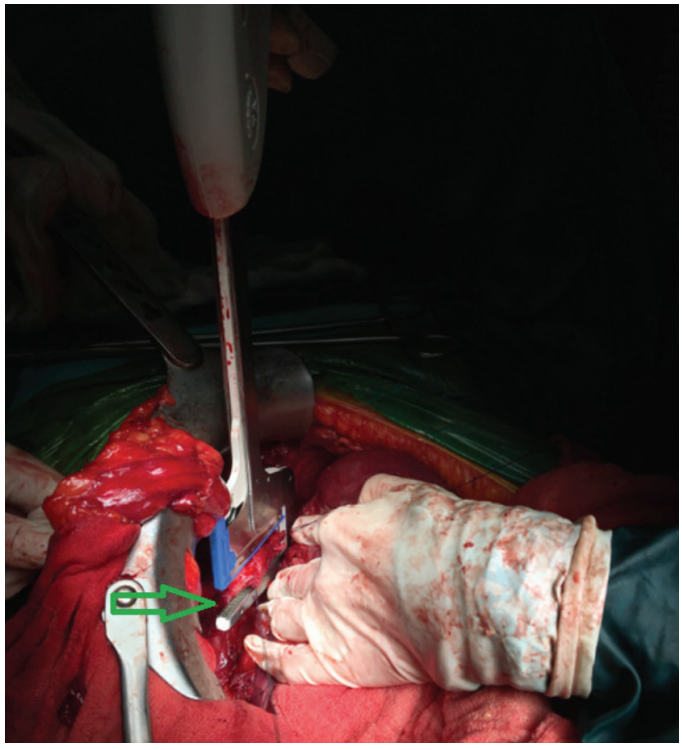


Figure 2. Thoraco-abdominal stapler (DST series™, 30 mm) was placed under the hauled full thickness implant transversally to diaphragm

effusion, and no pneumothorax. There was also no need for thoracentesis during the postoperative period in both patients in our institution. Diaphragmatic muscle invasion of a high-grade, serous ovarian carcinoma was reported in pathologic results [institutional review board (approval number: 07/2019/90057706-799)].

One of the concerns when undertaking diaphragmatic full thickness implant resection is pulmonary complication. Additionally, entrance to the pleural cavity increases the possibility of prophylactic chest tube application (4,5). The technique described here may have an advantage in minimizing the occurrence of pneumothorax and the amount of pleural effusion by avoiding pleural entrance. Thus, this may encourage less use of a prophylactic chest tube, decrease the need for thoracentesis, and also lessen postoperative morbidity. Our technique may also make diaphragmatic full thickness implant resection viable as part of minimally invasive surgeries. The undeniable fact that the operation time is longer in the presence of diaphragmatic full thickness implant resection in contrast to striping, because of the need for manual closure by suture. This technique may have an additional advantage in decreasing operation time because of automatically suturing. Kapnick et al. (6) showed that the probability of pleural/parenchymal involvement was higher in the presence of more than 5 cm full thickness implant. Therefore, we believe that this technique may be a good option in <4 cm full thickness implants.

To the best of our knowledge, this is the first report of the usage of a thoraco-abdominal stapler for resection of diaphragmatic full thickness implant without entrance to the pleural space. Diaphragmatic full thickness implant resection with stapler appears to be safe, practical and an easy to learn surgical technique. There is a need for large scale studies to evaluate the conclusions of this technique.

Günsu Kimyon Cömert, Alper Karalok, Ciğdem Kılıç, Derman Başaran, Fatih Kılıç, Osman Türkmen, Taner Turan

Clinic of Obstetrics and Gynecology, University of Health Sciences Turkey, Ankara Etlik Zübeyde Hanım Women's Health Training and Research Hospital, Ankara, Turkey

References

1. Manning-Geist BL, Hicks-Courant K, Gockley AA, Clark RM, Del Carmen MG, Growdon WB, et al. Moving beyond "complete surgical resection" and "optimal": Is low-volume residual disease another option for primary debulking surgery? Gynecol Oncol 2018; 150: 233-8.
2. Tseng JH, Cowan RA, Zhou Q, Iasonos A, Byrne M, Polcino T, et al. Continuous improvement in primary Debulking surgery for advanced ovarian cancer: Do increased complete gross resection rates independently lead to increased progression-free and overall survival? Gynecol Oncol 2018; 151: 24-31.
3. Eisenkop SM, Spirtos NM. What are the current surgical objectives, strategies, and technical capabilities of gynecologic oncologists treating advanced epithelial ovarian cancer? Gynecol Oncol 2001; 82: 489-97.
4. Franssen B, Tabrizian P, Weinberg A, Romanoff A, Tuvin D, Labow D, et al. Outcome of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy on patients with diaphragmatic involvement. Ann Surg Oncol 2015; 22(5): 1639-44.
5. Chéreau E, Rouzier R, Gouy S, Ferron G, Narducci F, Bergzoll C, et al. Morbidity of diaphragmatic surgery for advanced ovarian cancer: retrospective study of 148 cases. Eur J Surg Oncol 2011; 37: 175-80.
6. Kapnick SJ, Griffiths CT, Finkler NJ. Occult pleural involvement in stage III ovarian carcinoma: role of diaphragm resection. Gynecol Oncol 1990; 39: 135-8.

Herlyn-Werner-Wunderlich Syndrome; laparoscopic treatment of obstructing longitudinal vaginal septum in patients with hematocolpos - a different technique for virgin patients

Gökhan Boyraz, Alper Karalok, Taner Turan, Nejat Özgül

Clinic of Obstetrics and Gynecology, University of Health Sciences Turkey, Ankara Etlik Zübeyde Hanım Women's Health Training and Research Hospital, Ankara, Turkey

Abstract

We aimed to define a new laparoscopic treatment approach for patients with hematocolpos and obstructed hemi-vagina due to longitudinal obstructing vaginal septum. This technique is particularly useful for patients who desire to preserve virginity. To the best of our knowledge this is the first case reporting laparoscopic resection of vaginal septum with an obstructed hemivagina and hematocolpos.

Keywords: Hematocolpos, longitudinal vaginal septum, Herlyn-Werner-Wunderlich Syndrome

Received: 06 March, 2019 **Accepted:** 18 August, 2019

Introduction

Herlyn-Werner-Wunderlich Syndrome is a rare congenital anomaly characterized by uterus didelphys with blind hemivagina and ipsilateral renal agenesis and was initially described by Herlyn and Werner in 1971. The true incidence of this anomaly is unknown, however it has been reported between 0.1% and 3.8% (1,2).

A 30-year-old patient presented with severe abdominal-pelvic pain and dysmenorrhea. Pelvic magnetic resonance imaging indicated a complete uterine septum coexisting with longitudinal obstructing vaginal septum that might cause hematocolpos. Unilateral renal agenesis was detected in computerized tomography urogram. She had not been sexually active and in spite of the severe pelvic pain she absolutely rejected vaginal surgery in order to preserve her hymeneal integrity and virginity. This situation forced the use of a laparoscopic approach. Therefore, we aimed to define a new laparoscopic treatment approach for the patients with hematocolpos and obstructed hemi-vagina due to longitudinal obstructing vaginal septum. This technique is particularly useful for patients who desire to preserve virginity. All of the techniques described previously were based on a vaginal approach and, to the best of our knowledge, this is the first case reporting laparoscopic resection of vaginal septum with an obstructed hemivagina and hematocolpos. This laparoscopic approach in patients with obstructing longitudinal vaginal septum with hematocolpos not only preserves hymeneal integrity but also enables definition of genital tract anomalies and coexisting anomalies exactly. The procedure consisted of two major steps (Video 1). Firstly, a transverse incision is made in the anterior vagina wall (Figure 1). Secondly, the longitudinal vaginal septum is resected (Figure 2) and transverse vaginal incision is closed with intra-corporeal suturing (Figure 3).

Conclusion

This first description of a laparoscopic approach seems to be an alternative treatment options in patients with hematocolpos, especially in those who desire to preserve virginity.

Address for Correspondence: *Gökhan Boyraz*
e.mail: gokhan.boyraz@gmail.com ORCID: orcid.org/0000-0001-6165-1497

Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2019.2019.0046

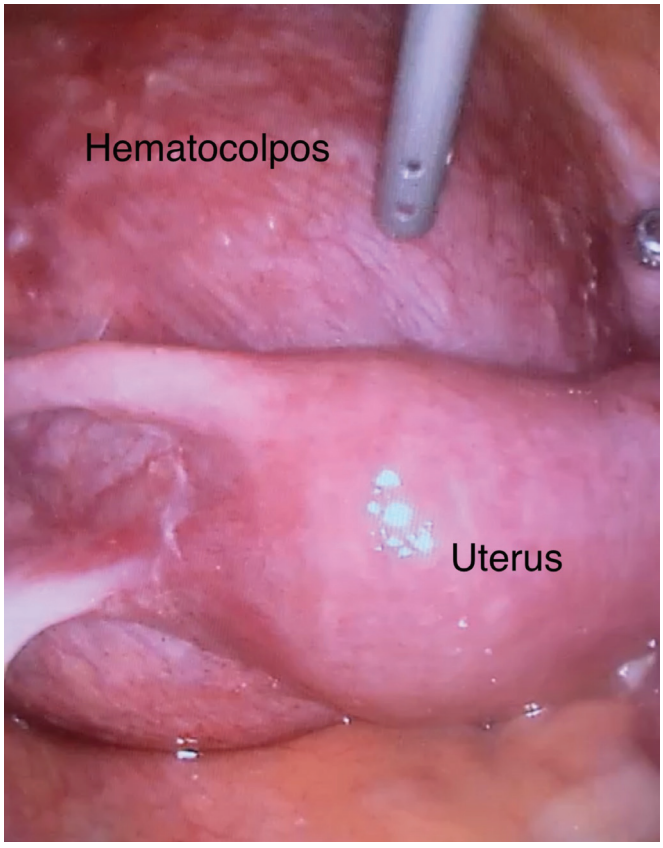


Figure 1. A wide hematocolpos corresponding to the obstructed left hemivagina

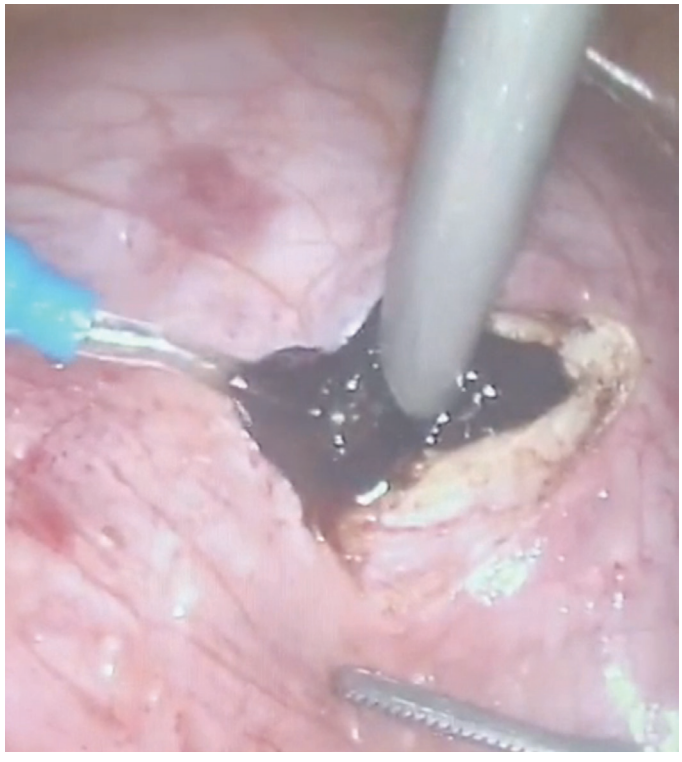


Figure 2. Draining the old menstrual blood

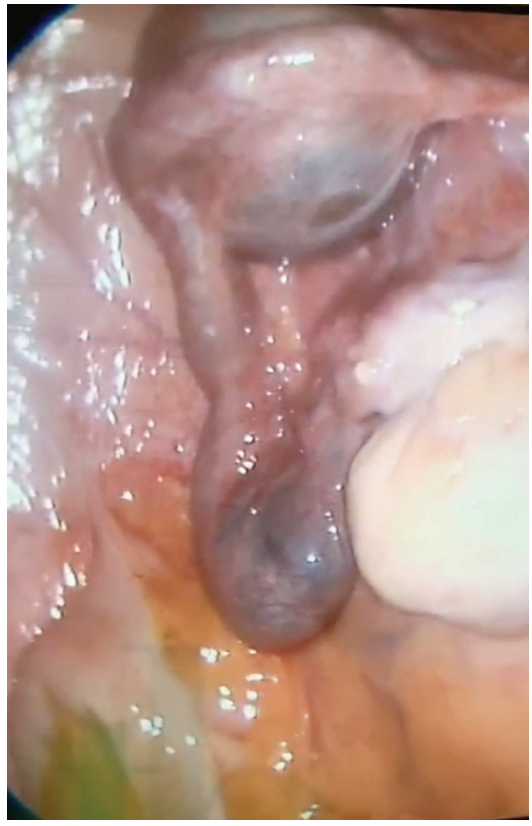


Figure 3. Fimbrial phimosis of left fallopian tube

Video 1. https://www.doi.org/10.4274/jtgga.galenos.2019.2019.0046.video1

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

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

References

1. Zhu L, Chen N, Tong JL, Wang W, Zhang L, Lang JH. New classification of Herlyn-Werner-Wunderlich syndrome. Chin Med J 2015; 128: 222-5.
2. Herlyn U, Werner H. Simultaneous occurrence of an open Gartner-duct cyst, a homolateral aplasia of the kidney and a double uterus as a typical syndrome of abnormalities. Geburtshilfe Frauenheilkd, 1971; 31: 340-7.

Use of a microsurgical vascular clip system (Yasargil clip) in laparoscopic fibroid enucleation

Shadi Younes[1], Julia Caroline Radosa[2], Anke Mothes[3], Bahriye Aktaş[1], Marc Philipp Radosa[1]

[1]Department of Obstetrics and Gynecology, Leipzig University Hospital, Leipzig, Germany
[2]Department of Obstetrics and Gynecology, Saarland University Hospital, Homburg, Germany
[3]Department of Obstetrics and Gynecology, St. George's University Hospital, Eisenach, Germany

Abstract

This video demonstrates the use of a microsurgical temporary vascular clip system to facilitate laparoscopic enucleation of uterine fibroids. Throughout the course of the last three decades, the laparoscopic route has been established as the approach of choice in the surgical treatment of uterine fibroids. Laparoscopic fibroid enucleation is characterized by a low morbidity rate and a high patient satisfaction level. Especially when treating a large fibroid or multiple fibroids, the well-vascularized myometrium can constitute a technical challenge in endoscopic fibroid enucleation. Diffuse bleeding may lead to significant intraoperative hemorrhage. The extensive use of bipolar or monopolar diathermy, in order to achieve hemostasis, might lead to post-operative uterine wall necrosis with a potential risk of uterine rupture during subsequent pregnancies. To address this clinical challenge, we developed a technique with temporary interruption of the uterine blood supply by applying a microsurgical vascular clip (Yasargil vascular clip system, Aesculap, Tuttlingen, Germany) to the uterine artery and the utero-ovarian vessel arcade to minimize bleeding during endoscopic fibroid enucleation.

Keywords: Yasargil clips, fibroid enculeation, laparoscopy

Received: 14 December, 2019 **Accepted:** 20 April, 2020

Introduction

The purpose of this video was to demonstrate the use of a microsurgical temporary vascular clip system to facilitate laparoscopic enucleation of uterine fibroids (Video 1).

Throughout the course of the last three decades, the laparoscopic route has been established as the approach of choice in the surgical treatment of uterine fibroids. Laparoscopic fibroid enucleation is characterized by a low morbidity rate and a high patient satisfaction level (1). Especially when treating a large fibroid, the well-vascularized myometrium can constitute a technical challenge in endoscopic fibroid enucleation. Diffuse bleeding may lead to significant intraoperative hemorrhage. The extensive use of bipolar or monopolar diathermy, in order to achieve hemostasis, might lead to post-operative uterine wall necrosis with a potential risk of uterine rupture during subsequent pregnancies (2).

To address this clinical challenge, we developed a technique with temporary interruption of the uterine blood supply by applying a microsurgical vascular clip (Yasargil vascular clip system, Aesculap, Tuttlingen, Germany) to the uterine artery and the utero-ovarian vessel arcade to minimize bleeding during endoscopic fibroid enucleation. Yasargil vascular clips were originally used in the treatment of intra-cranial aneurysms (3). In surgical gynecology, the Yasargil clip has been introduced for the treatment of vascular injuries during laparoscopic procedures (4).

The procedure was carried out under general anesthesia and the patient was placed in a dorsal lithotomy position. A Verres needle was introduced subumbilically and the abdomen was inflated with carbon dioxide to a pressure of 8 mmHg. We used low-pressure laparoscopy in order to minimize post-operative pain (5). Upon installation of the pneumoperitoneum, a 12 mm trocar was inserted subumbilically for the video laparoscope (0

Address for Correspondence: *Marc Philipp Radosa*
e.mail: Marc.Radosa@gesundheitnord.de ORCID: orcid.org/0000-0001-6695-3910

Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.
DOI: 10.4274/jtgga.galenos.2020.2020.0046

degree Endoeye, Olympus, Shinjuku, Japan) and three 5 mm ports were inserted in the left, middle and right lower abdominal quadrant, respectively. The peritoneal cavity was inspected and the uterine fibroid was identified. Then, the peritoneum on the left pelvic brim was incised laterally to the external iliac artery and medially to the ligamentum ovarii suspensorium to access the retroperitoneum. The left uterine artery and the left ureter were identified by blunt dissection and a temporary 15 mm Yasargil clip (Yasargil clip system, FT 280T; Aesculap, Tuttlingen, Germany) with a clamp force of 0.88 Newton was applied to the uterine artery, lateral to the ureter (Figure 1). This step was repeated on the contralateral site. The additional uterine blood supply, via the utero-ovarian vessel arcade, was occluded by placing a Yasargil clip on the ovarian ligament on each side (Figure 2). All four Yasargil clips are marked with a vicryl suture to facilitate identification towards the end of the surgery. The uterine serosa and the myometrium were subsequently incised and the surface of the fibroid was exposed. The lower middle 5 mm port was replaced by a 10 mm port and the fibroid was grasped with 10 mm tenaculum forceps. Then the fibroid was extracted from surrounding myometrium by blunt dissection. Closure of the uterus was achieved by interrupted, intra-corporeal double-layer sutures. A first stich was used to close the deep uterine muscle layer, while the following back-stich was used to close the superficial uterine muscle layer and the uterine serosa (Figure 3). Following the closure of the uterus, the Yasargil clips were removed, both peritoneal incisions were closed by continuous suture and the blood circulation of the uterus was photo documented. Fibroids were morcellated, using an electric morcellator (Storz, Tuttlingen, Germany) and extracted through the midline trocar and at the end of the procedure an intra-abdominal drain (French gauge 18) was placed for postoperative monitoring purposes.

Written informed consent was obtained from the patient for publication of this video and any accompanying images.

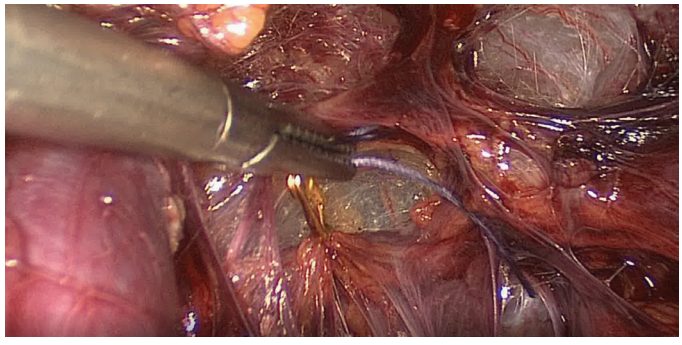


Figure 1. The left uterine artery and the left ureter are identified by blunt dissection and a Yasargil clip is applied to the uterine artery

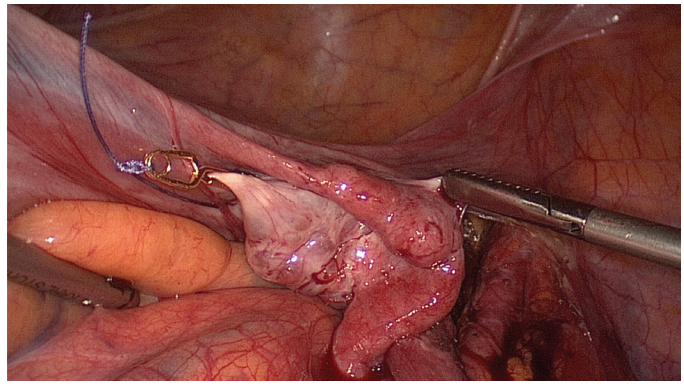


Figure 2. Additional uterine blood supply via the utero-ovarian vessel arcade is occluded by placing a Yasargil clip on the ovarian ligament of each side

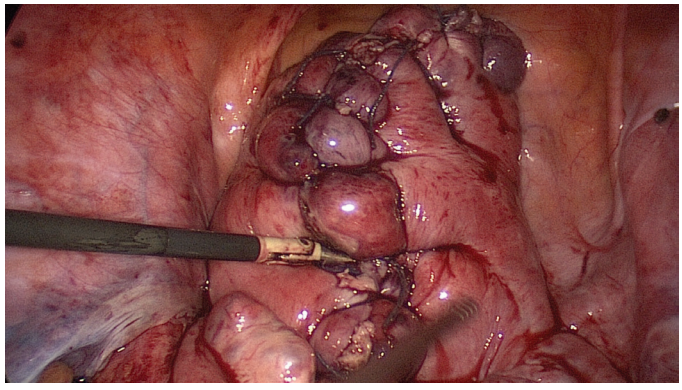


Figure 3. Reconstruction of the uterine wall: a first stich is used to close the deep uterine muscle layer, while the following back-stich is used to close the superficial uterine muscle layer and the uterine serosa

Video 1. https://www.doi.org/10.4274/jtgga.galenos.2020.2020.0046.video1

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

Financial Disclosure: *This study was financially supported by a grant from Saarland University Hospital; Saarland University grant number: HOMFOR2016 T201000789.*

References

1. Radosa MP, Winzer H, Mothes AR, Camara O, Diebolder H, Weisheit A, et al. Laparoscopic myomectomy in peri- and post-menopausal women is safe, efficacious and associated with long-term patient satisfaction. Eur J Obstet Gynecol Reprod Biol 2012; 162: 192-6.
2. Bernardi TS, Radosa MP, Weisheit A, Diebolder H, Schneider U, Schleussner E, et al. Laparoscopic myomectomy: a 6-year follow-up single-center cohort analysis of fertility and obstetric outcome measures. Arch Gynecol Obstet 2014; 290: 87-91.
3. Yaşargil MG. A legacy of microneurosurgery: memoirs, lessons, and axioms. Neurosurgery 1999; 45: 1025-92.
4. Chiantera V, Erdemoglu E, Vercellino G, Straube M, Schneider A. Laparoscopic management of external iliac artery injury using yasargil clamps and intracorporeal suture. J Minim Invasive Gynecol 2011; 18: 516-9.
5. Radosa JC, Radosa MP, Schweitzer PA, Radosa CG, Stotz L, Hamza A, et al. Impact of different intraoperative CO2 pressure levels (8 and 15 mmHg) during laparoscopic hysterectomy performed due to benign uterine pathologies on postoperative pain and arterial pCO2: a prospective randomised controlled clinical trial. BJOG 2019; 126: 1276-85.

2020 Referee Index

Acknowledgements for the Year 2020
(Reviewers contributed at the review process in 2020)

On behalf of the office staff and the Editorial Board of the *Journal of The Turkish German Gynecological Association*, we would like to thank to all of our reviewers of the past year for their outstanding contributions. Their thorough reviews and expertise enable our journal to improve its scientific quality. We certainly look forward to their ongoing support, suggestions and recommendations as to how to continue to advance the overall quality of the *Journal of The Turkish German Gynecological Association*.

Abdullah Karaer
Abdurrahman Hamdi İnan
Adnan Orhan
Agnieszka Nowak
Ahkam Göksel Kanmaz
Ahmed Abbas
Ahmed Maged
Ajit Sebastian
Alev Özer
Alex S. R. Souza
Alexandros Fotiou
Ali Anğın
Ali Gökçe
Ali Yavuzcan
Alper Şişmanoğlu
Amir Sohrabi
Amos Grunebaum
Anastasia Prodromidou
Andrew Monda
Anne Tardieu
Antonio Simone Laganà
Anuka Chonishvili
Anupama Bahadur
Arezoo Esmailzadeh
Asghar Tofighi
Ashish Verma
Aslı Yarcı Gürsoy
Asya Osborn
Ayla Sargın Oruç
Ayse Nur Aksoy
Ayşe Çitil
Azadeh Akbari Sene
Bahram Jamali
Barış Ata
Bartosz Pasnik
Batuhan Turgay
Bogdan Socea
Bolanle O. Ibitoye
Bukunmi Michael Idowu
Bulut Varlı
Burak Bayraktar
Burcu Bayoğlu
Bülent Çakmak
Bülent Yılmaz
Byron Asimakopoulos
C. S. Biyani
Camran Nezhat
Can Benlioğlu
Catalin-Bogdan Coroleuca
Cavit Kart
Cem Demirel
Cenk Yaşa
Chandan Das
Cihan İnan
Cihan Karadağ
Cihan Kaya
Çağatay Taşkıran
Dave Listijono
Defne Engür
Derman Başaran
Dubravko Habek
Duygu Altın
Ekrem Tok
Elif Ağaçayak
Emrah Beyan
Emre Göksan Pabuççu
Emre Günakan
Emre Karaşahin
Esra Yaprak
Everett F. Magann
Faik Mümtaz Koyuncu
Fatemeh Samieerad
Fatih Aktoz
Fatma Beyazıt
Fernanda Bertuccez Cordeiro
Fırat Tülek
Firoozeh Mirzaee
Forough Mortazavi
Fred Morgan-Ortiz
G. Bianchi
Gabriele Tonni
Gamze Nur Cimilli Şenocak
George Gitas
Gian Franco Zannoni
Giovanni Scambia
Giovanni Sisti
Giuseppe Rizzo
Gizem Bektaş
Gökçen Örgül
Gulzhanat Aimagambetova
Gülnaz Şahin
Gülşah Aynaoğlu Yıldız
Güray Tuna
Hadijat Raji
Hakan Çökmez
Hale Göksever Çelik
Harun Egemen Tolunay
Hasan Yüksel
Igor Lakhno
İbrahim Yalçın
İhsan Bağlı
İlker Kahramanoğlu
İlker Selçuk
İncim Bezircioğlu
Jitti Hanprasertpong
Jon I. Einarsson
Jose Marcos Sanches
Jule Eric
Julie S. Townsend
Kaan Baydemir
Kadir Bakay
Kadir Çetinkaya
Kadriye Erdoğan
Kazibe Koyuncu
Kemal Beksaç
Kerem Doğa Seçkin
Kiper Aslan

2020 Referee Index

Krzysztof Nowosielski
Laganà Antonio Simone
Leila Allahqoli
Lekha Saha
M. Ludovisi
M. Maliqueo
Mahmut Kuntay Kokanalı
Maja Avramovska
Manisha Beck
Marc Radosa
Maryam Razavi
Matthias David
Maureen Tigga
Mefkure Eraslan Şahin
Mehmet Özeren
Mert Turgal
Michal Kovo
Mika Gissler
Mine İslimye Taşkın
Miraç Özalp
Mohammed Ahmed Elmetwally
Murat Gültekin
Murat Öz
Murat Seval
Mustafa Kaplanoğlu
Mustafa Kara
Mustafa Zelal Muallem
Nadire İdil
Nalini Modepalli
Nefise Nazlı Yenigül
Niyazi Tuğ
Oluwagbemiga Oluwole Ayoola
Ozhan M. Turan
Ömer Tapısız
Önder Çelik
Özgüç Takmaz
Özgür Koçak
Pariseema S. Dave
Parul Arora
Pınar Gülşen Çoban
Pınar Hasdemir
Raziye Desdicioğlu
Razvan Derihaci
Rekha Bharti
Remzi Atılgan
Resul Arısoy
Riddhima Jain
Rimpy Tandon
Robert S. Ohgami
Runa Kara
S. Tahmina
Salih Taşkın
Salvatore Giovanni Vitale
Samia Husain
Sarvpreet Singh Ghuman
Seda Şahin Aker
Selver Akkaya
Serenat Eriş Yalçın
Sezin Ertürk
Shikha Jain
Shinya Matsuzaki
Sinem Sudolmuş
Sumanta Saha
Şafak Hatırnaz
Şafak Yılmaz Baran
Temitope Okunola
Tinatin Gagua
Tjokorda Gede Pemayun
Tolga Karacan
Tomoyasu Kato
Torstein R. Meling
Tuğba Kınay
Turhan Aran
Ümit Görkem
Vaidyanathan Gowri
Vakkas Korkmaz
Vorapong Phupong
Xuefeng Lu
Yasemin Doğan
Yavuz Emre Şükür
Yusuf Tohma
Yusuf Üstün
Zehra Özkan
Zeynep Tırmıkçıoğlu
Zohre Khoshnood

2020 Subject Index

2020 Subject Index

2020 Author Index

2020 Author Index

2020 Author Index