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galenos yayınevi

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Contact

Çetin Emeç Bulvarı Hürriyet Caddesi Harbiye Mahallesi 1/13 Öveçler, Ankara, Turkey
Phone: +90 312 481 06 06 Fax: +90 312 481 28 28 E-mail: editor@tjod.org

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e-mail: erkan@galenos.com.tr

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

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

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

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The "Turkish Journa The "Turkish Journal of Obstetrics and Gynecology (ISSN 1305-4252)" is the official publication of the Turkish Society of Obstetricians and Gynecologists. The journal is published quarterly (January, April, June and October) in English and publishes original peer-reviewed articles, reviews, case reports and commentaries in the fields of gynecology, gynecologic oncology, endocrinology and reproductive medicine and obstetrics. The journal will give publication priority to original research articles over case reports. 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 on the topic of the review 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.

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Cover letter to the editors addressing the following points:

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· Clinical trial registration, if applicable.

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

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

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

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

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

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

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

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

Manuscript Structure

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

Title Page

A separate title page should list;

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

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

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

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

Precis

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

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

Abstract

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

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

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

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

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

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

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

Key Words

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

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

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

Table 1. Manuscript length at a glance

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

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

Original researches should have the following sections;

Introduction

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

Material and Methods

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

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

Results

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

Discussion

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

Study Limitations

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

Conclusion

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

Conflict of Interest

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

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

References

References are numbered (Arabic numerals) consecutively in the order in which they appear in the text (note that references should not appear in the abstract) and listed double-spaced at the end of the manuscript. The preferred method for identifying citations in the text is

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using within parentheses. Use the form of the "Uniform Requirements for Manuscripts" (http://www.icmje.org/about-icmje/faqs/icmje-recommendations/). If number of authors exceeds seven, list first 6 authors followed by et al.

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

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

Examples

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

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

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

Tables and Figures

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TURKISH JOURNAL OF OBSTETRICS AND GYNECOLOGY

CONTENTS

TURKISH JOURNAL OF OBSTETRICS AND GYNECOLOGY

LETTER FROM THE PRESIDENT

Dear Colleagues,

As the spring is coming so does the meetings. Obstetrics and Gynecology meetings are mostly in spring or autumn. As TSOG we are going to have local meetings, in Adana, Şanlıurfa, İstanbul Anadolu, Ankara, İzmir, Mersin and many cities.

In March, we are going to have a Contraception meeting in Sapanca.

TSOG Ankara and Health Ministry and Health Unions came together, discussed the problems of Obstetrics and Gynecology Specialists and assistant and made a declaration and it was sent to Health Ministry to find solutions.

In a congress, I met the wife of Turkey's Prime Minister Sare Davutoğlu, MD. She is also an Obstetrician. I wanted a meeting with her and she kindly accepted. As the session was about high Cesarean rates. I have said that as TSOG we do not want high Cesarean rates as well. It is not the fault of Obstetricians only. In order to decrease the higher rates we think that: Performance points of the Obstetricians must be increased to vaginal deliveries (actually for all items), malpractice during vaginal delivery must be covered by Health Ministry and it is going to be a guarantee for us, midwifery must be supported. Health Ministry was very successful in Cigarette Stopping Campaign, in order to raise the awareness of the women, there must be media campaign in TV, Radio, etc for vaginal delivery.

She was interested and I requested her help to make a workshop in this subjet with Health Ministry for Cesarean rates, she said she is going to help.

I hope Obstetrics and Gynecology will regain its popularity soon for the assistants.

Please do not forget that there is always brightness at the and of darkness.

Cansun Demir, Prof. MD
President of TSOG

TURKISH JOURNAL OF OBSTETRICS AND GYNECOLOGY

EDITORIAL

Dear Colleagues,

I am proud to announce that our journal is now being indexed in the Web of Science in the category of ESCI. As our impact factor is increasing we are planning to apply to be indexed in PubMed.

As we have announced, our Editorial Board met on 10.1.2016 to set new criteria to become a member of the board for TJOG.

As we are the journal of our distinguished society, all colleagues who meet the criteria are welcome to be a member of the board. Becoming member of the board is not a lifetime duty. In the aim of being competitive, board members also set criteria for themselves to continue being a member. These criteria, besides being competitive, will provide a healthy turnover for new coming successful scientists to take over our editorial roles. Our criteria to meet this aim are set out below:

Aside from providing prestige, the role of the editorial board is to advise and support the editor.

Identifying new topics for commissions, special editions, and advising on direction for the journal, giving feedback on past issues and making suggestions for both subject matter and potential authors.

Provide content by writing occasional editorials and other short articles.

Approaching potential contributors.

Peer review-also help to identify peer reviewers and provide second opinions on papers (i.e. where there is a conflict between reviewers).

Identify appropriate conferences for editors to attend.

Endorse the journal to authors, readers, and subscribers, and encourage colleagues to submit their best work.

At the end of each year, each member of the Editorial Board will be scored against these criteria and the top 12 will be section Editor or associate Editor. The others will serve as members of the board having fulfilled previously announced minimum criteria for becoming board members.

I would like to thank Evrim Erdemoğlu MD for his work on setting these criteria for the Editorial Board. My idea is that the Editor in Chief should be selected by the board after election.

Best Wishes.

Eray Çalışkan MD,
Editor in Chief

Clinical Investigation / Araştırma

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Turk J Obstet Gynecol 2016;13:1-6

Characteristics and outcomes of in vitro fertilization in different phenotypes of polycystic ovary syndrome

Farklı polikistik over sendromunun fenotiplerinin in vitro fertilizasyon özellikleri ve sonuçlarının karşılaştırılması

Selçuk Selçuk[1], Enis Özkaya[1], Ahmet Eser[1], Melda Kuyucu[1], Hüseyin Tayfun Kutlu[1], Belgin Devranoğlu[1], Kenan Sofuoğlu[2], Vedat Erkan Dayıcıoğlu[1]

[1]*Zeynep Kamil Women and Children's Diseases Education and Research Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Turkey*

[2]*Medistate Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Turkey*

Abstract

Objective: The aim of this study was to investigate whether polycystic ovary syndrome (PCOS) phenotype without polycystic ovaries (PCO) differs in terms of in vitro fertilization (IVF) outcomes compared with classic phenotypes.

Materials and Methods: This retrospective controlled study included 262 patients who underwent IVF treatment with an indication of unexplained or tubal factor infertility (control group), ovulatory patients with PCO morphology (group 1), PCOS phenotype with oligoanovulation and hyperandrogenemia (group 2), PCOS phenotype with PCO morphology and oligoanovulation (group 3). Outcomes and baseline characteristics of IVF-embryo transfer treatments were compared among all groups.

Results: PCOS phenotype without PCO morphology had similar IVF stimulation characteristics compared with classic phenotypes; however, a higher total gonadotropin dose was needed to achieve similar results compared with patients with PCO morphology with or without PCOS. Basal follicle-stimulating hormone level (beta coefficient=0.207, p=0.003), group (beta coefficient=-0.305, p<0.001) and age (beta coefficient=0.311, p<0.001) were significantly associated with the total gonadotropin dose. The number of good quality embryo on transfer day was significantly lower in patients with isolated PCO morphology and PCO morphology with oligoanovulation than in those with PCOS phenotype without PCO morphology.

Conclusion: PCO morphology provides easier stimulation, whereas hyperandrogenemia provides better results as good quality embryos. However, the end point is similar in terms of biochemical, clinical, and ongoing pregnancy rates.

Keywords: Polycystic ovary syndrome, IVF, phenotypes

Öz

Amaç: Bu çalışmada polikistik over sendromunun (PKOS) farklı fenotiplerinin in vitro fertilizasyon (İVF) sonuçlarının karşılaştırılması amaçlandı.

Gereç ve Yöntemler: Bu retrospektif çalışmaya IVF tedavisi uygulanmış açıklanamayan veya tubal faktör infertilitesi olan hastalar (kontrol grup), polikistik over (PKO) morfolojisi olan ovulatuar hastalar (grup 1), oligo-anovulasyonu ve hiperandrojenemisi olan PKOS'lu hastalar (grup 2), PKO morfolojisi ve oligo-anovulasyonu olan hastalar (grup 3) olmak üzere toplam 262 hasta dahil edildi. Gruplar uygulanan İVF-embriyo transferi tedavisinin özellikleri ve sonuçları açısından karşılaştırıldı.

Bulgular: PKO morfolojisi olmayan PKOS'lu olgular; klasik PKOS fenotipi olan olgularla karşılaştırıldığında benzer over stimulasyon özellikleri göstermektedir ancak PKO morfolojisi olan olgulara göre daha yüksek gonadotropin dozu gerekmektedir. Bazal folikül uyarıcı hormon düzeyi (beta kat sayısı=0,207, p=0,003), grup (beta kat sayısı=-0,305, p<0,001) ve yaş (beta kat sayısı=0,311, p<0,001) toplam gonadotropin dozuyla istatistiksel olarak anlamlı derecede ilişkili bulundu. İzole PKO morfolojisi olan olguların ve oligo-anovulasyonu olup PKO morfolojisi olan olguların transfer günü iyi kalite embriyo sayısı, PKO morfolojisi olmayan PKOS'lu olgulara göre istatistiksel olarak anlamlı düzeyde daha düşük tespit edildi.

Sonuç: PKO morfolojisinin varlığının over stimulasyonunu kolaylaştırdığı, hiperandrojeneminin de embriyo kalitesi üzerine olumlu etkilerinin olduğu saptandı. Ancak gruplar arasında; biyokimyasal gebelik, klinik gebelik ve devam eden gebelik oranları açısından fark tespit edilmedi.

Anahtar Kelimeler: Polikistik over sendromu, IVF, fenotip

Address for Correspondence/Yazışma Adresi: Selçuk Selçuk, MD,
Zeynep Kamil Women and Children's Diseases Education and Research Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Turkey
Phone: +90 532 163 04 88 **E-mail:** md_sel@hotmail.com

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Introduction

Polycystic ovary syndrome (PCOS) is a complex disorder and may present in different phenotypes. Previous data included only the classic phenotype characterized by chronic anovulation and hyperandrogenism[1-3]. However, accumulated data led to the Rotterdam criteria, which allows for different PCOS phenotypes[4]. According to the defined criteria, four different phenotypes can be introduced: I. Hyperandrogenism, chronic anovulation, and polycystic ovaries (PCO); II. Hyperandrogenism and chronic anovulation but normal ovaries; III. Hyperandrogenism and polycystic ovaries but ovulatory cycles; and IV. Chronic anovulation and polycystic ovaries but no clinical or biochemical hyperandrogenism. A meta-analysis concluded that unknown intra-or extraovarian abnormalities may interfere with granulosa cell-oocyte interaction, oocyte maturation, and potential embryonic development and result in unsuccessful artificial reproduction techniques in PCOS[5]. However, it is not known whether different phenotypes of PCOS have similar results. It is well known that PCOS is associated with elevated adrenal androgens such as dehydroepiandrosterone sulphate (DHEAS) in 20-50% of cases and meta-analyses about the effect of DHEAS supplementation in assisted reproduction revealed improvement of oocyte production and pregnancy rates[6-9]. However, according to the aforementioned data, we know that all PCOS phenotypes do not have hyperandrogenemia or even PCO morphology, so is it possible to generalize all in vitro fertilization (IVF) outcomes in PCOS by assessing a mixture of women with different PCOS phenotypes?

In this study, we aimed to assess IVF characteristics among different PCOS phenotypes to show whether PCO morphology or hyperandrogenemia would interfere with the results.

Materials and Methods

Study population

Between 2009 and 2014, among the women referred to the infertility unit of the Department of Obstetrics and Gynecology, Zeynep Kamil Women and Children's Health Training and Research Hospital, 262 patients who underwent IVF treatment with an indication of unexplained or tubal factor infertility (control group, n=84), ovulatory patients with isolated PCO morphology (group 1, n=85), PCOS phenotype with oligoanovulation and hyperandrogenemia (group 2, n=38), PCOS phenotype with PCO morphology and oligoanovulation (group 3, n=55) were enrolled in the study (Table 1). Sample size was calculated according to the study by Kim et al.[10] with 95% confidence interval (CI) and 80% power. The exclusion criteria were age ≥40 years; body mass index (BMI) >35 kg/m^2; basal follicle-stimulating hormone (FSH) level >12 mIU/mL; presence of endometriosis; three or more previous unsuccessful IVF treatment; and systemic illness or endocrine disorders such as hyperprolactinemia, hypothyroidism, Cushing's syndrome and non-classic congenital adrenal hyperplasia. The groups were compared in terms of basal clinical characteristics and IVF outcomes. PCO morphology was determined based on the data from transvaginal ultrasound showing the presence of 12 or more peripherally-oriented cystic structures in one ultrasonographic plane, each of which measured 2 to 10 mm in diameter[11]. Oligo-anovulation was described as progesterone <3 ng/mL (<9.54 nmol/L) on days 18-21 and/or a menstrual cycle of longer than 35 days. Patients with an elevated serum testosterone >60 ng/dL (>2.08 nmol/L) and/or serum Δ4A levels >3.8 ng/mL were considered to have biochemical hyperandrogenemia and subjects with a Ferriman Gallwey score >8 were accepted as having clinical hyperandrogenemia[12]. The study protocol was approved by the Local Ethics Committee of Zeynep Kamil Research and Teaching Hospital.

Treatment protocol

On cycle day 3, ovarian stimulation was started by daily injection of recombinant FSH (r-FSH) (Gonal-F, Merck Serono, İstanbul, Turkey) with a starting dose specific for cases according to their age, BMI, ovarian reserve, and antral follicle count (AFC). According to the antagonist protocol, gonadotropin-releasing hormone (GnRH) antagonist (Cetrotide; 0.25 mg; Merck Serono, İstanbul, Turkey) injection was started from the 6th day of stimulation. Monitorization of the cycles was based on the ultrasound examination to record the number and size of the follicles and the double-layer endometrial thickness. For each participant on cycle days 2-3, transvaginal ultrasound was performed to determine AFC and screen for ovarian cysts. A repeat examination was performed on day 6 of stimulation and subsequently every 1-3 days as clinically indicated until the criterion for subcutaneous administration of recombinant chorionic gonadotropin alpha 250 mg (Ovitrelle; Merck-Serono, İstanbul, Turkey) was reached; at least two follicles ≥17 mm in diameter. Ovum retrieval was performed 36 h later. In all cases, an intracytoplasmic sperm injection procedure was performed on the same day (day 0) and embryo transfer was performed on day 3, 4 or 5 based on the quality of embryos. From the day of ovum retrieval, the luteal phase was supported by progesterone intravaginally (Crinone 8% gel; Serono, İstanbul, Turkey) twice a day.

Assessment of embryo quality

Table 1. Clinical characteristics of patients according to rotterdam criteria in each group

	Polycystic ovary morphology	Oligo anovulation	Clinical and/or biochemical hyperandrogenism
Group 1	+	-	-
Group 2	-	+	+
Group 3	+	+	-

Embryo quality was described according to the blastomeres size and number, the degree of fragmentation, and the presence of multinucleated blastomeres. Embryos with 4 or 5 equal- sized blastomeres and less than 10% cytoplasmic fragmentation with no multinucleation were accepted as good quality on day 2. An embryo with 7 or 8 equal-sized blastomeres with less than 10% cytoplasmic fragmentation and no multinucleation was accepted as good quality on day 3. A good quality embryo on day 4 was determined with following characteristics: embryo cavitation with compacted properties without morphologic anomalies such as vacuolation, excessive fragmentation, large number of excluded cells, and self-cavitation of cells[13,14]. On day 5, blastocyst quality and expansion were described in accordance with the classification of Gardner and Schoolcraft[15] and good quality embryo was accepted as ≥grade 3AA.

In vitro fertilization treatment outcomes

Chemical pregnancy was defined as positive β-hCG test following embryo transfer. Clinical pregnancy was defined as presence of gestational sac with fetal cardiac activity under ultrasonography. An ongoing pregnancy was defined as a pregnancy ≥12 weeks of gestation confirmed with ultrasonographic examination. Data of pregnancy outcomes were obtained from the hospital database or the pregnant women via phone. The implantation rate was calculated by dividing the number of gestational sacs with fetal cardiac activity by the number of embryos transferred. The primary end-points of the study were the chemical pregnancy rate, the clinical pregnancy rate, and ongoing pregnancy rate. Secondary outcomes evaluated were the total gonadotropin dose used, estradiol (E2) level on the trigger day, peak estradiol level, number of dominant follicles, number of metaphase II (MII) oocytes, MII oocytes rate, and implantation rate.

Statistical analysis

Statistical analysis was performed using SPSS version 11.5 software. All data were summarized using descriptive statistics, correlation analyses were used to show associations, multivariate regression was used to show adjusted associations, receiver operating characteric curve analysis was used to calculate predictive value, and the sensitivity and specificity. One-way ANOVA and Pearson's Chi-square tests were performed where appropriate; p=0.05 was accepted as the degree of significance. Data were given as mean ± standard deviation or percentage.

Results

The baseline clinical characteristics of all groups are given in Table 2. There were no significant difference in terms of age, BMI, basal FSH, E2 levels, and duration of infertility among all groups. The characteristics of IVF cycles of patients are detailed in Table 2. The total gonadotropin dose was similar between group 2 and the control group, whereas it was significantly lower in groups 1 and 3 than in other groups (p_1=0.002, p_2<0.001, p_3=0.006). Basal FSH level (beta coefficient=0.207, p=0.003), group (beta coefficient=-0.305, p<0.001) and age (beta coefficient=0.311, p<0.001) were significantly associated with the total gonadotropin dose. There was significant correlation between total gonadotropin dose and age (r=0.303, p<0.001), AFC (r=-0.553, p<0.001), basal FSH level (r=0.243, p<0.001), and group (r=-0.243, p<0.001). Age (AUC=0.595, =0.009) and basal FSH level (AUC=0.646, p<0.001) were found as significant predictors for the high gonadotropin dose >1800 IU, detrimented by the median level (Figure 1). The cut-off value for age was 29.5 years with 58% sensitivity and 54% specificity. The cut-off value for basal FSH was 6.2 with 65% sensitivity and 60% specificity. There were significantly higher numbers of oocytes retrieved in groups 1 and 3 when compared with patients in the control group; it was similar among groups 1, 2 and 3. There was no significant difference with respect to the ratio of MII oocytes and implantation rates among all groups. The number of good quality embryos on transfer day was significantly lower in patients in group 1 and 3 than in group 2. pregnancy rates are shown in Table 3. Biochemical, clinical and ongoing pregnancy rates were found similar among all groups.

Discussion

In the present study, we aimed to assess IVF characteristics among PCOS phenotypes with and without hyperandrogenemia or PCO morphology. Analyses of the data showed that IVF has similar success rates in patients with PCOS independent of presence or absence of hyperandrogenemia or PCO morphology. However, as expected, PCO morphology provided stimulation with lower doses and needed lower amounts of

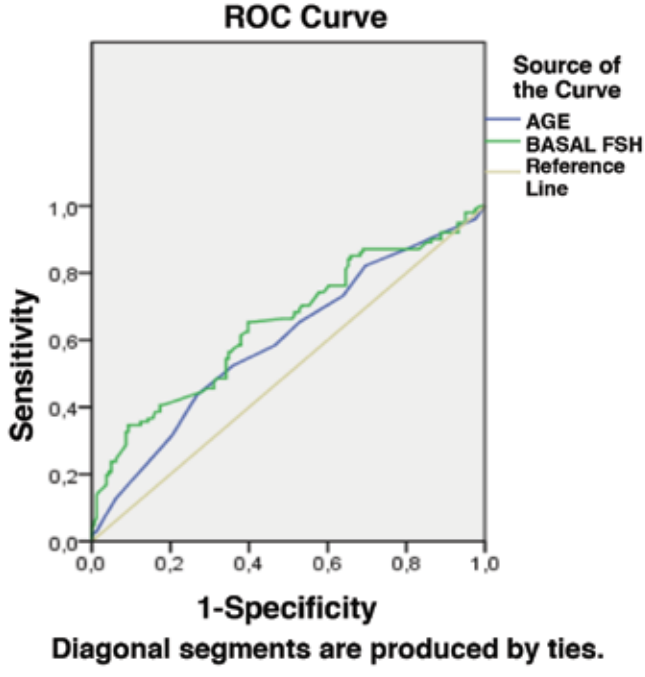

Figure 1. Receiver operating characteric curve of basal follicle stimulating hormone level and age to predict high gonadotropin dose

total gonadotropin dose. The number of good quality embryos was found to be significantly higher in the PCOS phenotype with oligoanovulation and hyperandrogenemia group. Despite the absence of PCO morphology, the numbers of dominant follicles were found comparable between this group and patients with PCO morphology. Good quality embryos and a comparable number of dominant follicles led us to conclude that hyperandrogenemia may have a favorable effect. However, this group needed a similar total gonadotropin dose when compared with the control group and higher total gonadotropin dose than the groups with PCO morphology. This shows that PCO morphology provides easier stimulation; hyperandrogenemia provides better results in terms of good quality embryos. Jamil et al.[16] compared the clinical and hormonal parameters among four phenotypes of PCOS based on the Rotterdam criteria and with a control group. Women in the oligo-anovulation and PCO group and in the control group had significantly lower levels of luteinizing hormone/FSH ratio, total testosterone, and free androgen index, and higher levels of FSH and sex hormone-binding globulin when compared with women in the oligo-anovulation, PCO and hyperandrogenemia groups[16]. In the literature, it was stated that androgens were found to have a favorable effect on follicle maturation, especially during the early stages[17]. However, other studies showed a negative effect of androgens on folliculogenesis and embryonic development[18]. Androgens have been suggested to have a modulating effect on FSH activity in developing granulosa cells, and studies on PCOS have shown that androgens have a positive and negative effect on folliculogenesis[17]. Despite the changing effects of androgens and PCO morphology among groups, the end point is similar in terms of biochemical, clinical, and ongoing pregnancy rates. A recently published study on the effect of PCO morphology on oocyte quality in intracytoplasmic sperm injection cycles compared with a control group showed neither positive nor negative effects and the MII oocyte number was found to be higher in the group with PCO morphology, whereas the ratio of MII oocyte was similar, the number of top quality embryos was comparable between groups but the implantation and clinical pregnancy rates were found significantly higher in the PCO morphology group[19]. The authors tried to assess the effect of PCO morphology alone on oocyte quality so their results were not consistent with ours because of the ignored effect of hyperandrogenemia, which was shown to have a favorable effect in our study. In addition, patients with PCOS had similar IVF outcomes compared with other hyperresponders without PCOS in a study by O'Neill et al.[20] Our study also produced similar end results but our data showed some critical cycle characteristics among different PCOS phenotypes. Ryan et al.[21] showed a negative effect of prolonged stimulation in assisted reproductive technology cycles but the authors claimed that this

Table 2. Comparison of baseline clinical characteristics among all groups

	Group 1 (n=85)	Group 2 (n=38)	Group 3 (n=55)	Control (n=84)	p
Age (years)	29.24±3.72	30.32± 4.07	29.01±3.84	30.38±4.03	NS
BMI (kg/m^2)	25.29±4.31	24.53±2.96	24.28±4.21	25.42±2.97	NS
Basal FSH (mIU/mL)	6.31±1.65	6.31±1.75	6.26±1.43	6.52±1.83	NS
Duration of infertility (years)	5.90±3.68	6.84±4.03	6.09±4.06	6.79±3.41	NS
Duration of stimulation (days)	8.54±1.19	8.64±1.32	8.75±1.73	8.76±1.64	NS
Total gonadotropin dose (IU)	1608.4±414.1	2135.5±956.9	1607.8±513.9	2307.4±1008.3	<0.001
E2 on hcg day (pg/mL)	2303.1±1098.5	2061.6±822.3	2116.9±1198.6	1913.6±992.1	NS
Peak E2 concentration (pg/mL)	2794.8±1460.2	2378.2±1662.5	2854.1±1802.7	2054.2±1145.4	0.003
EL on hcg day (mm)	9.86±1.81	10.28±2.09	9.57±1.74	10.07±1.79	NS
No of dominant follicle	7.88±3.19	7.84±3.26	7.74±3.76	6.85±2.97	NS
No of COC oocytes	12.37±4.66	10.68±4.62	11.41±5.69	9.20±4.51	<0.001
MII oocytes ratio (%)	77.86	77.79	74.26	77.93	NS
No of PNII	6.22±3.57	5.86±3.85	5.73±3.19	5.57±3.45	NS
Implantation rate (%)	35.52	32.89	32.08	19.92	NS
No of good quality embryo	1.60±1.56	3.76±2.71	1.46±1.18	3.01±2.02	<0.001
No of embryo transferred	1.18±0.44	1.21±0.41	1.14±0.45	1.24±0.48	NS

The level of significance was accepted at p=0.05 level, Data were given as mean ± SD and (%), BMI: Body mass index, FSH: Follicle stimulating hormone, EL: End line, COC: Cumulus-oocyte complex, MII: Metaphase II, PNII: two pro-nuclei, NS: Not significant, SD: Standard deviation, E2: Estradiol

effect was not observed in patients with PCOS. According to their article, PCOS had a different response to stimulation in a wide range, and to the best of knowledge, different phenotypes were not assessed separately. The effect of basal testosterone levels in IVF cycles of patients without PCOS was evaluated in a study by Sun et al.[22] consistent with our results in PCOS patients, the authors concluded that although basal testosterone did not predict pregnancy outcomes, it was associated with the large follicles on human koryonik gonadotropin day, FSH dosage, and also that lower levels of basal testosterone might be related with poor ovarian response[22]. Embryo cleavage kinetics were studied by Wissing et al.[23] with a small sample size. Contrary to our results, their study showed slower development to the 8-cell stage from fertilization in patients with hyperandrogenic PCOS[23]. An article published in 2014 compared cumulative live birth rates among groups of patients with PCOS, isolated PCO, and controls; their data revealed higher live birth rates in the group with isolated PCO compared with controls. This favorable outcome was not observed in the PCOS group and the authors claimed that this may be due to unfavorable embryo competence otherwise observed in PCOS[24]. Again, in their study a general conclusion was drawn from a mixture of patients with different PCOS phenotypes.

The limitations of our study were its retrospective nature and relatively small sample size. The importance of the present study is in the evaluation of assisted reproductive technology (ART) outcomes of different phenotypes of PCOS because there is limited data in the literature that compares subtypes of PCOS in terms of characteristics and outcomes of ART.

Conclusion

To the best of our knowledge, this is a unique study assessing IVF outcomes in different PCOS phenotypes in an acceptable number of participants. PCO morphology provides easier stimulation; hyperandrogenemia provides better results in terms of good quality embryos. Multivariate regression analyses showed that easier stimulation is based on basal FSH level, group, and age. However, the end point was similar regarding biochemical, clinical, and ongoing pregnancy rates.

Table 3. Comparison of outcomes of IVF cycles among all groups

	Group 1 (n=85)	Group 2 (n=38)	Group 3 (n=55)	Control (n=84)	p
Biochemical pregnancy rate*					
%	40.0	36.8	34.5	25.3	0.283
(n)	(34)	(14)	(19)	(21)	
Clinical pregnancy rate					
%	30.1	36.8	30.9	22.9	0.425
(n)	(25)	(14)	(17)	(19)	
Ongoing pregnancy rate					
%	24.1	25.0	23.6	20.5	0.930
(n)	(20)	(9)	(13)	(17)	

The level of significance was accepted at p=0.05 level, Chi square test was used, IVF: in vitro fertilization

Ethics

Ethics Committee Approval: The study protocol was approved by the Local Ethics Committee of Zeynep Kamil Training and Research Hospital, Informed Consent: A consent form was completed by all participants.
Peer-review: External and Internal peer-reviewed.

Authorship Contribtions

Surgical and Medical Practices: Hüseyin Tayfun Kutlu, Belgin Devranoğlu, Concept: Selçuk Selçuk, Enis Özkaya, Design: Selçuk Selçuk, Enis Özkaya, Hüseyin Tayfun Kutlu, Data Collection or Processing: Ahmet Eser, Melda Kuyucu, Analysis or Interpretation: Enis Özkaya, Literature Search: Selçuk Selçuk, Belgin Devranoğlu, Kenan Sofuoğlu, Writing: Selçuk Selçuk, Enis Özkaya.
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The outcomes of controlled ovarian hyperstimulation/ intrauterine insemination in patients with unilateral tubal occlusion on hysterosalpingograph

Histerosalpingografide tek taraflı tubal oklüzyon saptanan hastaların kontrollü ovaryan hiperstimulasyon/intrauterine inseminasyon sonuçları

Selçuk Selçuk[1], Mehmet Küçükbaş[1], İlter Yenidede[2], Semra Kayataş Eser[1], Ahmet Eser[1], Çetin Çam[1], Hüseyin Tayfun Kutlu[1]

[1]*Zeynep Kamil Women and Children's Diseases Education and Research Hospital, Clinics of Obstetrics and Gynecology, İstanbul, Turkey*

[2]*Fatih Sultan Mehmet Training and Research Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Turkey*

Abstract

Objective: The aim of the present study was to evaluate the pregnancy rates of intrauterine insemination (IUI) and controlled ovarian hyperstimulation (COH) in patients with one-sided tubal occlusion on hysterosalpingography (HSG).

Materials and Methods: Patients who underwent COH/IUI were enrolled into this retrospective cohort study. The patients with one-sided tubal occlusion diagnosed under HSG who met the inclusion criteria were accepted into the study group. The control group consisted of patients with unexplained infertility. The outcomes of COH/IUI were compared between the study and control groups.

Results: Ninety-seven patients in the study group (n=44) and control group (n=53) who underwent COH/IUI treatment were included into study. The biochemical, clinical, and ongoing pregnancy rates were similar between patients with unilateral occlusion diagnosed under HSG and those with unexplained infertility. The spontaneous pregnancy rate within one year was higher in patients with normal HSG than in patients with unilateral tubal occlusion, but the difference did not show statistical significance.

Conclusion: Infertile patients with one-sided tubal occlusion in HSG can be managed as with patients with unexplained infertility and normal HSG findings. In addition, COH/IUI may be considered as the first-line treatment option in the management of these patients.

Keywords: Unilateral tubal occlusion, infertility, intrauterine insemination

Öz

Amaç: Bu çalışmada histerosalpingografide (HSG) tek taraflı tubal oklüzyon saptanmış olan hastaların kontrollü ovaryan hiperstimülasyon (KOH) ve intrauterine inseminasyon (IUI) tedavisi sonrası gebelik oranlarını araştırmayı amaçladık.

Gereç ve Yöntemler: Bu retrospektif kohort çalışmaya KOH/IUI tedavisi alan hastalar dahil edildi. HSG'de unilateral tubal oklüzyon saptanmış hastalar çalışma grubu olarak kabul edildi. Kontrol grubu; açıklanamayan infertilite tanısı almış hastalardan oluşturuldu. Çalışma ve kontrol grupları KOH/IUI sonuçları açısından karşılaştırıldı.

Bulgular: Bu çalışmaya KOH/IUI tedavisi almış 97 hasta (çalışma grubu=44, kontrol grubu=53) dahil edildi. HSG ile tanı konulmuş tek taraflı tubal oklüzyonu olan hastalar ile açıklanamayan infertilitesi olan hastalar arasında biyokimyasal, klinik ve devam eden gebelik oranları benzer olarak bulundu. Kontrol grubunda, ilk yıl içinde spontan gebelik oranları çalışma grubuna göre daha yüksek olarak bulundu ancak bu fark istatistiksel olarak anlamlı değildi.

Sonuç: HSG'de tek taraflı tubal oklüzyon saptanan infertil hastalar, normal HSG bulgularına sahip infertil hastalar gibi yönetilebilirler. Ayrıca, belirtilen hasta grubunda KOH/IUI ilk tedavi seçeneği olarak düşünülebilir.

Anahtar Kelimeler: Tek taraflı tubal oklüzyon, infertilite, intrauterin inseminasyon

Address for Correspondence/Yazışma Adresi: Selçuk Selçuk, MD,
Zeynep Kamil Women and Children's Diseases Education and Research Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Turkey
Phone: +90 532 163 04 88 **E-mail:** md_sel@hotmail.com
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Introduction

Tubal disease is responsible for approximately 30-40% of female infertility[1]. Recently, the incidence of tubal factor has increased and has become a major cause of female infertility. The major risk factor for tubal factor infertility is pelvic inflammatory disease; other possible risk factors are history of tubal surgery and ectopic pregnancy[2]. Hysterosalpingography (HSG) and laparoscopy are the most common procedures used in the assessment of the tubal patency. HSG is usually the first preferred clinical tool because laparoscopy is more invasive and more expensive[3]. There is no consensus about the optimal management of patients with unilateral tubal occlusion. The assessment of tubal patency through laparoscopic chromotubation, intrauterine insemination with controlled ovarian stimulation (COH), and in vitro fertilization (IVF) are the recommended management options for these patients[4-6]. In the literature, there are insufficient data regarding the success rates of COH and IUI in the treatment of patients with unilateral tubal occlusion.

In the present study, we aimed to evaluate the pregnancy rates of COH/IUI in patients with unilateral tubal occlusion diagnosed under HSG.

Materials and Methods

This retrospective cohort study was conducted in Zeynep Kamil Tertiary Hospital between 2013 and 2015. The study protocol was approved by the Local Research and Ethics Committee of the institution. Demographic and clinical information of patients were abstracted from the hospital's database. Inclusion criteria were age ≥18 and <40 years, basal follicle-stimulating hormone (FSH) level <15 IU/mL, normal basal luteinizing hormone, body mass index <35 kg/m^2, normal semen parameters according to the World Health Organization (WHO) criteria, no presence of endocrine abnormalities, and no uterine cavity abnormalities[7]. Patients with unilateral tubal occlusion diagnosed under HSG and who met the inclusion criteria were accepted into the study group. The control group consisted of patients with unexplained infertility, normal HSG findings and those who met the same inclusion criteria. All patients underwent COH/IUI treatment.

In the ovarian stimulation protocol, subcutaneous injection of gonadotropins as recombinant FSH (Gonal F, Merck Serono, İstanbul, Turkey) with starting dose of 50-100 IU/day from the 2nd-4th day of the menstrual cycle was administered. Monitoring using transvaginal ultrasonography (TVU) was performed daily after the fifth day of stimulus. When ≥2 follicles reached a diameter of ≥17 mm, subcutaneous injection of recombinant chorionic gonadotropin alpha 250 mg (Ovitrelle; Merck-Serono, İstanbul, Turkey) was administered. A concentrated, washed sperm sample was prepared and IUI was performed 34-36 hours after human chorionic gonadotropin (hCG) injection. Primary outcomes were biochemical, clinical, and ongoing pregnancy rates. The secondary outcome was the spontaneous pregnancy rate. Patients were invited to the infertility clinic to measure the β-hCG value 15 days after IUI. Positive serum β-hCG levels as ≥10 mIU/L were regarded as biochemical pregnancy and presence of a gestational sac on ultrasonography was regarded as clinical pregnancy. Ongoing pregnancy was defined as a pregnancy ≥12 weeks of gestation. Spontaneous pregnancy was accepted as pregnancy without any treatment within one year after unsuccessful IUI.

Statistical Analysis

Statistical analysis was performed using SPSS version 15.0 software. Mann-Whitney U test and Pearson's Chi-square tests were performed where appropriate. A value of p=0.05 was accepted as the degree of significance. Data are given as mean ± standard deviation or percentage.

Results

Ninety-seven patients who met the inclusion criteria and underwent COH/IUI treatment were included in study. Forty-four patients with unilateral tubal occlusion were included into the study group and 53 patients with unexplained infertility were assigned as the control group. Comparison of baseline clinical characteristics and sperm parameters of the two groups are given in Table 1. There were no significant differences between the study and control groups. In addition, there were no significant differences regarding IUI cycle characteristics of patients when the two groups were compared (Table 1). The biochemical, clinical, and ongoing pregnancy rates of the two groups are given in Table 2. The biochemical, clinical, and ongoing pregnancy rates per cycle of study group were 13.6%, 11.4%, and 11.4%, respectively. The biochemical, clinical, and ongoing pregnancy rates of the control group were 9.4% for all parameters. There were no statistical differences between the two groups. The spontaneous pregnancy rates were found 15.9% and 18.9% for study group and control group, respectively, and there was no statistically significant difference.

Discussion

In present study, the biochemical, clinical, and ongoing pregnancy rates of COH/IUI treatment were similar between patients with unilateral occlusion and patients with unexplained infertility. In addition, the spontaneous pregnancy rate within one year after unsuccessful IUI treatment was higher in the control group than in the study group but the difference did not reach statistical significance.

The management of infertile patients showed differences based on their HSG findings. In general, patients with bilateral tubal occlusion can be referred to IVF treatment or for further evaluation for tubal patency with laparoscopic chromotubation. The management of patients with one-sided tubal occlusion is less clear[1,8].

In the literature, the diagnostic accuracy of HSG was evaluated in various studies. Mol et al.[9] conducted a prospective cohort study of 794 patients with the participation of 11 clinics

to evaluate the importance of HSG and laparoscopy for the prediction of fertility outcomes. The sensitivity and specificity of HSG was reported as 0.81 and 0.75, respectively, for any form of tubal occlusion at laparoscopic surgery.

The authors reported the adjusted fecundity rate ratios (FRR) for unilateral tubal occlusion diagnosed at HSG as 0.80 and for bilateral tubal occlusion as 0.49. Accordingly, the authors concluded that bilateral tubal occlusion significantly impaired fertility outcomes whereas unilateral tubal occlusion mildly reduced fertility outcomes. Diagnosis of occlusion at laparoscopy had a greater worsening effect on fertility outcomes (FRR=0.51 and 0.15 for unilateral and bilateral tubal occlusion, respectively) than those at HSG[9].

A retrospective study assessed the fertility prognosis of patients with tubal occlusion detected using HSG. The FRR of unilateral tubal occlusion was 0.81 and that of bilateral tubal occlusion was 0.30[10]. The authors suggested that patients with one-sided tubal pathology and patients with normal HSG findings had nearly similar fertility potential, but the presence of bilateral tubal pathology detected on HSG decreased fertility potential significantly. In our study, the spontaneous pregnancy rate of patients with normal HSG findings was higher than patients with one-sided tubal occlusion, but the difference was not found as statistically significant (18.9% vs. 15.9%, p>0.05).

In the literature, the success rates of COH/IUI in patients with diagnosis of unilateral tubal occlusion at HSG were assessed in different studies. In a retrospective study, Lin et al.[2] reported that the pregnancy rates per cycle of COH/IUI treatment for patients with one-sided tubal occlusion on HSG and those with normal HSG findings were 17.3% and 18.9%, respectively. The difference of pregnancy rates between the two groups showed no statistical significance. The authors stated that COH/IUI could be initial treatment options for infertile patients with unilateral tubal occlusion. Farhi et al.[11] assessed the cumulative pregnancy rates for three cycles of COH/IUI treatment among patients diagnosed as having one-sided tubal occlusion compared with patients with unexplained infertility (controls). The cumulative pregnancy rates were reported as 30.9% for the study group and 42.6% for the control group. The authors stated that there was no significant difference between the two groups in terms of cumulative pregnancy rates. Yi et al.[12] evaluated the outcomes of COH/IUI treatment among thirty-seven infertile women (52 cycles) with unilateral tubal occlusion compared with a control group that included patients with unexplained infertility. The pregnancy rate per cycle was 17.3% in patients with unilateral tubal occlusion and 16.5% in the control group without statistical significance. The outcomes

Table 1. Comparison of demographic and clinical characteristics between the two groups

	Study group (n=44) (mean ± SD)	Control group (n=53) (mean ± SD)	p
Age (years)	30.09±3.92	28.49±4.45	NS
Gravida	0.36±1.16	0.23±0.75	NS
Duration of infertility (years)	3.73±1.95	3.88±2.80	NS
Infertility type (%)			NS
Primary	90.9	90.6	
Secondary	9.1	9.4	
Basal FSH (mIU/mL)	7.34±1.96	7.27±1.75	NS
Basal E2 (pg/mL)	53.28±24.11	52.17±27.60	NS
Basal sperm concentration (10^6/mL)	50.05±31.68	60.1±31.02	NS
Basal total sperm count (10^6)	166.15±149.92	187.89±150.87	NS
Basal total sperm motility (%)	60.84±13.75	58.04±16.60	NS
Previous IUI cycles (no)	0.36±0.57	0.28±0.82	NS
Duration of stimulation (days)	8.43±2.78	7.82±2.41	NS
Total gonadotropine dose (IUI)	609.89±293.06	585.58±178.94	NS
No of dominant follicle	1.25±0.44	1.16±0.37	NS
EL on hCG day (mm)	9.47±2.36	7.90±1.59	NS

The level of significance was accepted at p=0.05 level, Data were given as mean ± SD and (%), FSH: Follicle stimulating hormone, EL: End line, No: Number, IUI: Intrauterine insemination, hCG: Human chorionic gonadotropin, SD: Standard deviation, NS: Not significant, E2: Estradiol

Table 2. Comparison of outcomes of intrauterine insemination cycles between two groups

	Study group (n=44)	Control group (n=53)	p
Biochemical pregnancy rate			
%	13.6	9.4	NS
(n)	(6)	(5)	
Clinical pregnancy rate			
%	11.4	9.4	NS
(n)	(5)	(5)	
Ongoing pregnancy rate			
%	11.4	9.4	NS
(n)	(5)	(5)	
Spontaneous pregnancy rate			
%	15.9	18.9	NS
(n)	(7)	(10)	

The level of significance was accepted at p=0.05 level, Chi-square test was used, NS: Not significant

of our study are similar with the literature. In the present study, the ongoing pregnancy rate per cycle of study group was 11.4% whereas the ongoing pregnancy rate per cycle of control group was 9.4%. The biochemical, clinical, and ongoing pregnancy rates per cycles did not show a significant difference between the study and control groups.

Conflicting results about the clinical importance of the site of tubal occlusion and outcomes of COH/IUI treatment are reported in different studies. Lower pregnancy rates are demonstrated in women with mid-distal or distal tubal occlusion than in women with proximal tubal occlusion[2,11,12]. Some authors stated that the site of tubal occlusion should be considered in the management of patients with unilateral tubal occlusion whereas others reported that the site of tubal occlusion had no importance in the management of these patients[2,11,12].

The relatively small sample size and retrospective nature of the study were the limitations of the present study.

Conclusion

Infertile patients with one-sided tubal occlusion on HSG can be managed as with patients with unexplained infertility and normal findings on HSG. In addition, COH/IUI may be considered as the first-line treatment option in the management of these patients.

Ethics

Ethics Committee Approval: The study protocol was approved by the Local Research and Ethics Committee of the institution, Informed Consent: This retrospective cohort study was conducted in Zeynep Kamil Tertiary Hospital between 2013 and 2015.
Peer-review: External and Internal peer-reviwed.

Authorship Contributions

Surgical and Medical Practices: Hüseyin Tayfun Kutlu, Concept: Selçuk Selçuk, Çetin Çam, Design: Selçuk Selçuk, Semra Kayataş Eser, Data Collection or Processing: İlter Yenidede, Mehmet Küçükbaş, Analysis or Interpretation: Çetin Çam, Literature Search: Ahmet Eser, Semra Kayataş Eser, Writing: Selçuk Selçuk, Hüseyin Tayfun Kutlu.
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Does screening for vaginal infection have an impact on pregnancy rates in intracytoplasmic sperm injection cycles?

Vajinal enfeksiyon taraması intrasitoplazmik sperm enjeksiyonu sikluslarındaki gebelik başarısını etkiler mi?

Özlem Eldivan[1], Özlem Evliyaoğlu[1], Ebru Ersoy[1], Gönül Aksu[2], Serdar Dilbaz[1], Ümit Göktolga[1]

[1]*Etlik Zübeyde Hanım Women's Healthcare Education and Research Hospital, Clinic of Obstetrics and Gynecology, Ankara, Turkey*

[2]*Etlik Zübeyde Hanım Women's Healthcare Education and Research Hospital, Clinic of Microbiology, Ankara, Turkey*

Abstract

Objective: Assisted reproduction techniques have become widespread worldwide. Considering their costs, physicians endeavor to improve pregnancy rates. Infections are one of the disrupting problems in this arena. We aimed to investigate the effects of screening for vaginal infection on pregnancy rates in intracytoplasmic sperm injection cycles.

Materials and Methods: One hundred twenty patients randomized into two groups for this study. Patients were screened for vaginal infections in group 1, and no screening was performed in group 2. The assisted reproduction outcomes were investigated and compared between the two groups.

Results: There was no significant difference between ages, or durations and causes of infertility of patients who conceived and of those who did conceive. Forty-five patients in group 1, and 40 patients in group 2 reached the embryo transfer stage. The rates of conception were 23.5% (n=4) in culture-positive patients (n=17), and 42.9% (n=12) in culture-negative patients (n=28) in group 1. There was no significant difference among patients who were not screened, screen-positive, and screen-negative, in terms of pregnancy rates. None of the patients had N*eisseria gonorrhoeae* or *Trichomonas vaginalis*. Bacterial vaginosis was detected in 13 patients, and both bacterial vaginosis and *Chlamydia trachomatis* were detected in 4 patients. Three of 4 patients who conceived screen-positive and 8 of 12 patients who conceived screen-negative delivered healthily at term.

Conclusion: No significant difference was found between patients who were sampled for culture and patients who were not sampled in terms of pregnancy rates. Also, no difference was found between the patients who were culture-negative and patients who were treated with antimicrobials after a culture positive result. Further larger studies are warranted to clarify this issue.

Keywords: Infection, screening, culture, assisted reproduction, pregnancy rates

Öz

Amaç: Yardımlı üreme teknikleri dünya çapında yaygınlaşmıştır. Maliyetlerini düşünerek, klinisyenler daha yüksek gebelik oranları elde etmeye çabalamaktadırlar. Çalışmamızda, bu konudaki sorunlardan birisi olan vajinal enfeksiyonların taranmasının intrasitoplazmik sperm enjeksiyonu sikluslarındaki gebelik başarısına etkilerini araştırmayı amaçladık.

Gereç ve Yöntemler: Her bir grupta 60 rastlantısal hasta olmak üzere, 2 grup halinde, 1. grup vajinal enfeksiyon taraması yapılan grup, 2. grup tarama yapılmayan grup olarak hastalar çalışmaya dahil edildi. Yardımlı üreme teknikleri sonuçları gruplar arasında karşılaştırıldı.

Bulgular: Gebe kalan ve kalmayan grup arasında yaş, infertilite süresi ve sebebi açısından fark gözlenmedi. Birinci gruptan 45, 2. gruptan 40 hasta embriyo transferi aşamasına ulaştı. Birinci grupta kültürde üremesi olan 17 hastadan 4'ü (%23,5), üremesi olmayan 28 hastadan 12'si (%42,9) gebe kaldı. Gebelik oranları açısından, taranmayan, kültürde üremesi olan ve olmayan grup arasında fark bulunmadı. Hastalardan hiç birinde *Neisseria gonorrhoeae* ve *Trichomonas vaginalis* yoktu. On üç hastada bakteriyal vajinozis, 4 hastada bakteriyel vajinozis beraberinde *Chlamydia trachomatis* tespit edildi. Kültürde üremesi olup gebe kalan dört hastadan üçü, üremesi olmayıp gebe kalan 12 hastadan 8'i miadında sağlıklı doğum yaptı.

Sonuç: Kültürle taranan ve taranmayan hastalar arasında gebelik oranları açısından fark bulunmadı. Ayrıca, üremesi olmayan grup ile üremesi olup da antimikrobiyallerle tedavi edilenler arasında da fark bulunmadı. Bu konuyu aydınlatmak için daha ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Enfeksiyon, tarama, kültür, yardımla üreme, gebelik oranları

Address for Correspondence/Yazışma Adresi: Ebru Ersoy, MD,
Etlik Zübeyde Hanım Women's Healthcare Education and Research Hospital, Clinic of Obstetrics and Gynecology, Ankara, Turkey
Phone: +90 505 455 82 12 **E-mail:** eebruersoy09@gmail.com
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PRECIS: No significant difference was found between patients who were sampled for culture and those who were not sampled in terms of pregnancy rates in intracytoplasmic sperm injection cycles.

Introduction

Significant increase in the number of couples seeking treatment for infertility. Their increased use has been associated with significant economic costs because they are expensive procedures. As stated in a study in the Netherlands, costs per cycle started at €2381 and €2578 for in vitro fertilization (IVF) and Intracytoplasmic sperm injection (ICSI), respectively[1]. The pregnancy rate in IVF programmes remains about 20-50% inspite of the high rate of successful fertilization. This has led to the proposition that additional factors critical for the implantation process must be limiting[2]. There is growing evidence that cervical-vaginal flora may strongly influence pregnancy rates. A few studies showed that the presence of microbial flora of the cervix on embryo transfer (ET) catheter was associated with poor IVF-ET outcomes[3-5]. *Chlamydia trachomatis (C. trachomatis)* and *Neisseria gonorrhoeae (N. gonorrheae)* are the most prevalent sexually-transmitted bacterial infections worldwide. Although most genitourinary tract infections of *C. trachomatis* in women are asymptomatic, it is a major public health problem because of the recent rises in the reported number of cases and the severe reproductive morbidity that results from untreated infections and associated costs to the health services[6]. However, bacterial vaginosis (BV) is being increasingly implicated in upper genital tract infections in women[7]. *Trichomonas vaginalis* is a far more prevalent sexually-transmitted infection than either *Chlamydia trachomatis* or *Neisseria gonorrhoeae*, yet in stark contrast, little attention is paid to trichomoniasis. It is suggested that it can reduce the chances of conception from both female and male factors and should be considered in the diagnostic tests of infertile couples[8].

The primary objective of our study was to investigate the effect of screening for vaginal infections on pregnancy success in patients undergoing ICSI in our clinics.

Materials and Methods

Women undergoing IVF at the Assisted Conception Unit of Etlik Zubeyde Hanim Women's Health Education and Research Hospital between April 2009 and June 2009 were recruited for this case-control study. Ethical approval for the study was obtained from the local ethics committee (approval date/number: 13.03.2009/7) and all participants gave their written consent to participate. The research was completed in accordance with the Declaration of Helsinki[9].

Women who had basal serum levels of follicle-stimulating hormone <10 mIU/L, prolactin, free triiodothyronine (fT_3), free thyroxine (fT_4), and thyroid-stimulating hormone levels within the normal range, aged <38 years, and asymptomatic for leukorrhea underwent a long luteal GnRH-analog protocol. Patients who had received antibiotic treatment during the previous three months were excluded from the study. All the enrolled women were informed that they had been investigated for sexually-transmitted microorganisms and had been thoroughly tested in accordance with our clinic protocol, which included a baseline early follicular phase endocrine profile, and baseline transvaginal ultrasonography including antral follicle count. Age, cause, and duration of infertility was recorded. On completion of the investigations, 60 patients were randomly assigned to the study group (group 1) and 60 patients to the control group (group 2). Randomization was based on computer-generated codes. In group 1, patients were screened for vaginal infections and no screening was performed in group 2. The women entered the study on the day of gonadotropin initiation. The women were treated with a conventional superovulation regimen of pituitary down-regulation followed by stimulation with gonadotropins.

Specimens were collected immediately after menses. Cultures for *N. gonorrhea* and *C. trachomatis* were collected separately from the endocervix and vaginal cultures were taken to investigate the presence of bacterial vaginosis and *Trichomonas vaginalis*. A non-lubricated bivalve speculum was inserted and the vaginal walls and posterior fornix were sampled using two sterile cotton swabs. One swab was rolled on a glass slide for Gram staining, and the flora were investigated for BV using Nugent's criteria. One swab was placed in aerobic transport media. A second droplet of discharge was mixed with saline on another slide for the wet mount. The wet mount was immediately examined to detect motile Trichomonas trophozoites. *C. trachomatis* was investigated via QuickVue test using as enzyme immunoassay (EIA). QuickVue is a rapid chlamydial antigen capture assay based on genus-specific murine monoclonal antibody. Specimens for N. gonorrhoeae were collected from the endocervix as described above. The specimens were immediately plated directly onto modified Thayer-Martin medium.

The time between obtaining the culture result and the day for oocyte pick up in each patient was at least 5 days because the cultures and gram stain were collected at the beginning of the IVF cycle after menses.

Patients were treated with proper antimicrobials according to the recommendations of the Center for Disease Control and Prevention (CDC) when organisms are detected. For bacterial vaginosis, 500 mg oral metronidazole (Flagyl) taken twice daily for 7 days and metronidazole intravaginal 0.75% gel were used. The recommended treatment for tichomoniasis was 2 g oral metronidazole (Flagyl) in a single dose. Oral azithromycin 1 g was scheduled for patients with *C. trachomatis* and a single oral 400-mg dose of cefixime was scheduled for patients with *N. gonorrhoeae*. The treatments were completed before oocyte pick-up.

When at least two leading follicles reached ≥18 mm in diameter, recombinant (rec) human Chorionic Gonadotropin (hCG Ovitrelle, Serono) was administered. Transvaginal ultrasound-guided oocyte retrieval was performed 34-36 hours after 0.25 mg rec hCG administration. Maximum 3 embryos were transferred on day 3 or 5 after oocyte retrieval. In both groups, good quality or blastocyst stage embryos were transferred. The luteal phase was supported with vaginal progesterone gel (Crinone 8%) administered daily starting on the day of oocyte pick-up.

Conception was defined as a positive hCG titer on day 12. We considered concentrations greater than 10 U/L as a positive result. Follow up ultrasound at 6 and 8 weeks of gestation confirmed clinical pregnancy. We followed all the women through to completion of the pregnancy.

The sample size of the study were calculated using G*Power (G*Power Ver. 3.00.10, Franz Faul, Üniversität Kiel, Germany) statistical package. The required sample size for 90% power, 5% Type I error, 10% Type II error and 20% effect size were calculated as 96 to better elucidate the impact of vaginal infection on pregnancy rates in intracytoplasmic sperm injection cycles. To protect the study from potential lost to follow-ups, we planned to enroll 120 patients.

The statistical analyses were performed using the Statistical Package for Social Sciences (version 11.5; SPSS Inc., Chicago). Descriptive data are expressed as mean ± standard deviation. Student's t-test or Mann-Whitney U test were used for the comparison between groups. Pearson's Chi-square and Fisher's exact tests were used to analyze categorical data. The level of significance was set at $p<0.05$.

Results

One hundred twenty patients who met the inclusion criteria were enrolled into the study. Eighty-five patients (70.8%) who underwent IVF reached the embryo transfer stage. The mean age of the patients was 31±6.1 years. Clinical indications included male factor infertility in 56 (46.7%) cycles, ovulatory dysfunction in 24 (20.9%), unexplained infertility in 15 (12.5%), and tubal factor infertility in 6 (5%) cycles.

There was no significant difference between the ages of patients who conceived and those who did not conceive. Likewise, the two groups of patients were similar regarding the duration of infertility. Six of 25 women (24%) with unexplained infertility, 18 of 37 women (48.6%) with male factor infertility, and 6 of 23 (26.1%) women with other causes of infertility conceived successfully, but there was no difference among causes of infertility regarding the rates of pregnancy (p=0.077) (Table 1).

In group 1 (n=60), 45 patients underwent ET procedure. The rate of conception was 23.5% (n=4) in those with positive culture (n=17), and 42.9% (n=12) when no microorganism was detected (n=28). In group 2 (n=60), 40 patients reached ET. Of these 40 patients, conception was achieved in 35.0% (n=14). There was no significant difference between groups 1 and 2 in conception rates (p=0.96), and there was no difference among the groups of screen-positive, screen-negative, and not screened with culture, in terms of pregnancy success (p=0.42) (Table 2).

None of the patients had *N. gonorrhoeae* or *Trichomonas vaginalis*. Bacterial vaginosis was detected in 13 patients, and in 4 patients both bacterial vaginosis and *C. trachomatis* were recovered (Table 3).

Three of four patients who were screen-positive conceived and continued their pregnancy until a successful and healthy term delivery, but one spontaneously lost her pregnancy at six weeks of gestation. Eight of 12 patients who were screen-negative conceived and continued their pregnancy until a successful and healthy term delivery.

Table 1. Distributions and comparisons of age, duration of infertility, and cause of infertility in patients who did and did not conceive

Variables	Pregnancy absent	Pregnancy present	p value
Age (years)	30.5±5.8	31.2±6.4	0.567
Duration of infertility (years)	7.7±5.0	7.4±4.6	0.879
Cause of infertility			0.077
Unexplained (n=25)	19 (76.0%)	6 (24.0%)	
Male factor (n=37)	19 (51.4%)	18 (48.6%)	
The others (n=23)	17 (73.9%)	6 (26.1%)	

Table 2. Screening with culture and its association with pregnancy rates

Variables	Pregnancy absent (n=55)	Pregnancy present (n=30)	p value
Groups			0.96
Not screened (n=40)	26 (65.0%)	14 (35.0%)	
Screened (n=45)	29 (64.4%)	16 (35.6%)	
Groups			0.42
Not screened (n=40)	26 (65.0%)	14 (35.0%)	
Culture negative (n=28)	16 (57.1%)	12 (42.9%)	
Culture positive (n=17)	13 (76.5%)	4 (23.5%)	

Table 3. Conception rates according to the cultured microorganism

	Bacterial vaginosis (n=13)	Bacterial vaginosis and chlamydia trachomatis (n=4)	p value
Conception			0.999
Negative	10 (76.9%)	3 (75.0%)	
Positive	3 (23.1%)	1 (25.0%)	

Discussion

We have shown that there was no difference betwen the groups of screen-positive, screen-negative and not screened in culture in terms of pregnancy success in our study population.

In previous studies, Chlamydial antibodies were found significantly higher in patients who attended clinics for tubal factor infertility and were candidates for IVF than patients who attended for other causes of female infertility[10-12]. Gaudoin et al.[10] concluded that bacterial vaginosis and prior chlamydial infections had a significant association with tubal factor infertility, but were no associated with IVF outcomes in their study in 1999. However, in our study, these infections could not be accused for tubal factor infertility because the patients who were treated with IVF accounted for a small number. Chlamydial infections detected by favor of chlamydial antibodies were found not to effect IVF outcomes and embryonic implantation in a study by Osser et al.[11] that included 121 women with tubal infertility. Also, in our study, chlamydial infections detected using EIA were found not to effect IVF outcomes.

Apart from this, several different studies investigated the effects of lower genital tract infections on female infertility. Spandorfer et al.[13] studied the prevalence of bacterial vaginosis and abnormal bacterial vaginal microenvironment in infertile women, and cervical inflammatory cytokines caused by abnormal vaginal flora were found to be high in patients who presented Wilson with unexplained infertility; however, no effect was found on IVF outcomes[14]. In another study by Wilson et al.[14] bacterial vaginosis was shown to be more frequent in patients undergoing IVF because of tubal infertility than in patients with other causes of infertility; these findings support the association among bacterial vaginosis, pelvic inflammatory disease, and tubal damage. Furthermore, in that study, bacterial vaginosis was detected more frequently in women undergoing IVF owing to anovulation, and hormones were shown to have effects on vaginal flora[14]. Our study failed to show these effects because of the low number of patients. Ralph et al.[15] found that bacterial vaginosis had no effect on pregnancy rates, but had abortifacient effects in the first trimester of pregnancy in their large study that included 867 infertile women who presented for IVF. Additionally, bacterial vaginosis was found to be associated with endometritis and preterm labor in a study by Korn et al.[16].

The transmissive effects of bacterial vaginosis for sexually-transmitted diseases were studied by Yoshimura et al.[17] with a sample of 406 patients. *C. trachomatis* was more frequently detected in patients with bacterial vaginosis than in those without. In the same study, young women were shown to be more inclined to bacterial vaginosis and sexually-transmitted diseases, especially Chlamydial cervicitis. In our study, there was no difference between the ages of women who were culture-positive and culture-negative. However, in our study, all patients who had Chlamydial infection also had bacterial vaginosis, and our results were similar with that study.

Wittemer et al.[18] tried to determine the effects of treatment of vaginal and endocervical infections on IVF outcomes. The authors concluded that suspending the actual IVF cycle seemed more reasonable because of the possible deleterious effects of infection on embryonic implantation process, even if the patient was treated with a proper antimicrobial agent. Selim et al.[19] stressed that women with bacterial vaginosis and with a decreased vaginal concentration of hydrogen peroxide-producing lactobacilli may have decreased conception rates and increased rates of failed pregnancy. Liversedge et al.[20] stated that giving treatment for bacterial vaginosis before IVF could only be useful to lower the late pregnancy complications because there has been no confirmed effects of bacterial vaginosis on the rates of fertilization and implantation. However, in our study, there was no difference between the pregnancy rates of patients screened and not screened with culture, although lower pregnancy rates were detected in patients who were culture-positive.

The small number in our study group, and the subsequent scarcity of the patients who attended for IVF, and additionally, the unavailability of embryo transfer for every patient prevents us from being able to express the association between the types of infectious microorganisms and the etiology of infertility. A confirmatory culture was not taken after treatment. These represent the limitations of our study.

In conclusion, this study was performed to investigate whether endocervical and vaginal infections had any effects on pregnancy rates in IVF cycles. The patients who underwent endocervical and vaginal culture were compared with patients who had no culture. No significant difference was found between the patients who were sampled for culture and patients who were not sampled in terms of pregnancy rates. Also, no difference was found between patients who were culture-negative and those who were treated with antimicrobials after a culture-positive result.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the local ethics committee (approval date/number: 13.03.2009/7) and all participants gave their written consent to participate. The research was completed in accordance with the Declaration of Helsinki.

Peer-review: External and Internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Gönül Aksu, Serdar Dilbaz, Concept: Özlem Eldivan, Özlem Evliyaoğlu, Design: Özlem Eldivan, Ebru Ersoy, Data Collection or Processing: Özlem Eldivan, Analysis or Interpretation: Özlem Evliyaoğlu, Ümit Göktolga, Literature Search: Özlem Evliyaoğlu, Ebru Ersoy, Writing: Özlem Eldivan, Özlem Evliyaoğlu, Ebru Ersoy.

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What is the optimal strategy in the management of patients with preterm premature rupture of membranes before 32 weeks of gestation?

Otuz iki haftadan önce preterm erken membran rüptürü ile başvuran hastaların yönetiminde optimal strateji nedir?

Bilge Çetinkaya Demir, Kiper Aslan, Mehmet Aral Atalay

Uludağ University Faculty of Medicine, Department of Obstetrics and Gynecology, Bursa, Turkey

Abstract

Objective: Our aim was to compare the outcomes of expectant management of pregnancy or immediate delivery in patients with preterm premature rupture of membranes (PPROM) between $24+^0$ and $32+^0$ weeks of pregnancy.

Materials and Methods: This is a retrospective cohort study conducted at a tertiary medical center. Patients who were diagnosed as having PPROM between $24+^0$ and $32+^0$ weeks of gestation were selected from an electronic database. Thirty-one patients with expectant management and 22 patients with spontaneous immediate delivery were analyzed. Birth weight, Apgar score, duration of stay in the neonatal intensive care unit (NICU), composite adverse outcomes, and mortality rates of groups were compared. Binary logistic regression analysis with backward stepwise elimination was used to determine confounding factors for antenatal complications and neonatal composite adverse outcomes.

Results: Gestational age at admission was smaller in the expectant management group. The median latency period was 6 days (range, 2-58 days). Although gestational age at delivery was similar, birth weights were smaller in expectant management group compared with the immediate delivery group ($p=0.264$ and $p<0.05$, respectively). Apgar scores, duration in the NICU, composite adverse outcomes, and neonatal mortality rates were similar in each group. Antenatal complication in the expectant management group was higher ($p<0.05$). Gestational age at delivery and serum C-reactive protein levels were two confounding factors for antenatal complication and gestational age at delivery was the only factor affecting composite adverse outcome.

Conclusion: Expectant management in patients with PPROM at 24 to 32 gestational weeks might be considered as a good alternative.

Keywords: Chorioamnionitis, prematurity, latency period, expectant management

Öz

Amaç: Yirmi dört ile 32 hafta arasında preterm erken membran rüptürü (PEMR) ile başvuran hastalardan hemen doğuran grup ile takip edilen grubun sonuçlarının kıyaslanması amaçlanmıştır.

Gereç ve Yöntemler: Çalışmamız üçüncü basamak bir hastanede yapılmış retrospektif kohort çalışmadır. Yirmi dört ile 32 hafta arasında PEMR ile başvuran gebelerin verilerine elektronik veri sisteminden ulaşılmıştır. Başvuru sonrasında hemen doğrumuş 22 hasta ile takip sonrasında doğuran 31 hastanın maternal ve yenidoğan verileri kıyaslanmıştır. Doğum kilosu, Apgar skorlaması, yenidoğan yoğun bakım ünitesinde (YDYB) kalma süresi, kötü yenidoğan sonuçları ve ölüm sıklığı her iki grup için kıyaslanmıştır. Lojistik regresyon analizi ile antenatal ve yenidoğan sonuçlarının karıştırıcı ve etkileyici faktörleri araştırılmıştır.

Bulgular: Takip altına alınan hastaların başvuru anındaki gebelik haftası hemen doğuran hasta grubundan daha küçük idi. Ortalama bekleme süresi 6 (2-58) gün idi. Doğumdaki gebelik haftası her iki grup için benzer olmasına karşın, yenidoğanların doğum kiloları takip edilen grupta hemen doğuran gruba göre daha küçük bulundu ($p=0,264$ ve $p<0,05$, sırasıyla). Apgar skorları, YDYB'da kalış süresi, kötü yenidoğan sonuçları ve yenidoğan mortalite oranları her iki grup için benzerdi. Antenatal komplikasyon sıklığı takip grubunda daha fazla bulundu ($p<0,05$). Doğumdaki gebelik haftası ve C-reaktif protein değerleri antenatal komplikasyon için ve doğumdaki gebelik haftası ise kötü yenidoğan sonuçları için belirleyici faktörler olarak bulundu.

Sonuç: Yirmi dört-32 hafta arası PEMR ile başvuran gebelerde hastanın takip altına alınması yenidoğan sonuçlarına olumsuz etki yapmamaktadır ve uygun bir yaklaşım olarak hastaya sunulabilir.

Anahtar Kelimeler: Koryoamnionit, premetürite, bekleme süresi, takip

Address for Correspondence/Yazışma Adresi: Bilge Çetinkaya Demir, MD,
Uludağ University Faculty of Medicine, Department of Obstetrics and Gynecology, Bursa, Turkey
Phone: +90 224 295 25 16 **E-mail:** bilgecd@yahoo.com
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Introduction

Rupture of fetal membranes before the 37th week of gestation is defined as preterm premature rupture of membranes (PPROM) and is related with a high-risk perinatal period. PPROM occurs in approximately 3% of all pregnancies[1]. The most important factor that determines the risk of perinatal morbidity and mortality is gestational age at delivery[2]. Perinatal mortality is higher in cases of PPROM before the 32nd gestational week[3]. Thus, trying to postpone the delivery is the main concern in these cases by expectant management. There are various studies regarding this issue. Use of antibiotics and corticosteroids and periodic assessment of fetal wellbeing following hospitalization are suggested management plans for these cases[3]. Nevertheless, PPROM could increase maternal and fetal risks such as intrauterine infections, maternal sepsis, neonatal sepsis, and fetal demise[3]. Therefore, there is a delicate balance between the benefits and risks of expectant management. With expectant management there is no consensus on the optimal delivery time, latency period, and frequency of assessment. The duration of the expectant period ranges from 7 to 10 days in different studies[4]. Randomized trials with regard to expectant management generally compare pregnancies between 34 and 37 weeks[5]. In this study, we aimed to compare expectant management with immediate delivery of fetuses and to assess which strategy was optimal in management of patients with PPROM between the 24th and 32nd weeks of gestation because the data in the literature concerning expectant management during this period is not strong. Additionally, we tried to determine factors that interfere with maternal and neonatal morbidity and mortality in this period of pregnancy.

Materials and Methods

This study is a retrospective cohort study conducted in a tertiary medical center. The delivery data between January 2009 and January 2015 was retrieved from the hospital's electronic database and patients who were admitted with a symptom of amniotic fluid gush between the 24th and 32nd weeks of gestation were enrolled.

PPROM was defined as rupture of membranes before the 37th week of gestation; the diagnosis was established in the patient history through speculum examination or placental alpha microglobulin-1 protein (AmniSure, Qiagen Sciences, Germantown, MD, US) testing of vaginal discharge. Gestational age was calculated using the last menstrual period or through first trimester fetal crown-rump length measurement. Patients with placental abruption, chorioamnionitis diagnosed at admission, pre-eclampsia, multiple pregnancies, fetal intrauterine growth retardation, and fetal congenital and chromosomal abnormalities were excluded from study. All patients who were diagnosed as having PPROM between gestational weeks 24 and 32 were hospitalized. Patients were treated with intravenous antibiotics (ampicillin 1 gr, i.v., q.i.d. for 7 days) and antenatal corticosteroid (betamethasone, 12 mg i.m., twice dose at a 24-hours apart). Clinical parameters and laboratory parameters of chorioamnionitis including white blood cell (WBC) counts and C-reactive protein (CRP) testing were evaluated. Tocolysis was administered for only 48 hours during the corticosteroid administration period. Calcium channel blockers and beta-adrenergic receptor agonists are the two preferred tocolytics in our institution. If the patient was in true labor and delivered within 24 hours of admission despite tocolysis, they were included in the immediate delivery group. Patients who did not deliver spontaneously within 24 hours of admission were included in the expectant management group. For the latter group after initial evaluation, maternal fever and heart rate were measured every 6 hours and WBC counts and CRP were monitored every other day. Patients in the expectant management group were not treated with tocolysis beyond 48 hours. Fetal wellbeing was assessed on a daily basis using electronic fetal monitoring and ultrasonography.

Latency period was defined as the time elapsed between onset of PPROM to delivery. The latency period was then divided into 2 subgroups for assessment of clinical outcomes as follows; 1) ≤7 days of latency and 2) >7 days of latency. Delivery eventuated spontaneously or was indicated for non-reassuring fetal status, abdominal pain, placental abruption, and clinical signs or when laboratory findings of chorioamnionitis were observed. Chorioamnionitis was diagnosed on a clinical basis with maternal fever (>38 °C), leukocytosis, uterine tenderness, fetal tachycardia or foul-smelling amniotic fluid with no other source of infection. The attending obstetrician determined the type of delivery depending on patient's obstetrics history and fetal status.

Antenatal complications that were evaluated in our study included chorioamnionitis, abruption of placenta, and cesarean section due to acute fetal distress or umbilical cord prolapse.

Following delivery, neonates were assessed by a neonatologist and hospitalized for clinical evaluation. Neonatal data including birth weight, Apgar scores, duration of stay in the neonatal intensive care unit (NICU), and composite adverse outcome and mortality were reviewed. Composite adverse outcome comprised conditions such as respiratory distress syndrome (the presence of two or more of the following criteria: evidence of respiratory compromise, a persistent oxygen requirement for more than 24 h, administration of an exogenous surfactant and radiographic evidence of hyaline membrane disease), intraventricular hemorrhage, retinopathy of prematurity, necrotizing enterocolitis and sepsis (proven by bacterial culture of clinical highly suspected sepsis).

Data analysis was performed using SPSS software version 22 (SPSS Inc, Chicago, IL). Continuous data are given in mean with standard deviation or median with minimum and maximum values depending on the distribution characteristics. Categorical data are presented as the number of patients or percentage as appropriate. Student's t-test and Chi-square tests were used

for comparisons between the groups. Binary logistic regression analysis with backward stepwise elimination was used to determine confounding factors for antenatal complications and neonatal composite adverse outcomes. A p value of <0.05 was considered significant.

Results

During the study period, among the 993 preterm deliveries performed in our institution, 90 were diagnosed as PPROM between the 24th and 32nd gestational weeks. Fifty-three patients remained in the final analysis after application of exclusion criteria (Figure 1).

Among the 53 patients, 22 delivered within 24 hours (immediate delivery group) and 31 patients were managed expectantly. The maternal characteristics were similar in both groups (Table 1). Median maternal age of the immediate delivery group and expectant management group was 30 years (range, 18-37 years) and 30 years (range, 21-42 years), respectively. Gestational age at admission was 218 days (range, 182-224 days) for the immediate delivery group and 189 days (range, 168-224 days) for the expectant management group (p<0.05). The mean WBC and C-reactive protein measurements were similar in each group at admission. For the expectant management group, the median interval time was 6 days (range, 2-58 days). Gestational age at delivery was similar; 218 days (range, 182-224 days) for the immediate delivery group and 207 days (range, 176-267 days) for the expectant management group. There was no fetal demise.

There were more antenatal complications in the expectant management group compared with the immediate delivery group (48% vs 18%, respectively) (p<0.05) (Table 1). However, patients with a latency period >7 days did not have significantly increased maternal complication rates compared with patients with a latency period of ≤7 days (40% vs 56%, respectively) (p=0.479) (Table 2). No patients delivered due chorioamnionitis with <7 days of latency. Three out of 6 patients with a latency period >7 days delivered due to chorioamnionitis. Two patients were delivered due to non-reassuring fetal status.

Antenatal complication was a dependent variable, and gestational age at admission, gestational age at delivery, interval day, WBCs at delivery and CRP at delivery were independent variables in the binary logistic regression analysis. Gestational age at delivery and CRP levels at delivery were found to be 2 confounding factors for increased antenatal complications (Predicted logit of antenatal complication=8.637+(-0.046) x gestational age at delivery + 0.162 x (CRP at delivery) (Omnibus test of model: p<0.001; Nagelkerke R Square=0.251; Hosmer-Lemeshow goodness of fit test p=0.487).

Neonatal birth weight was larger in the immediate delivery group compared with the expectant management group (1613±452 g vs. 1274±429 g, respectively). First and 5th minute Apgar scores were similar for both groups (Table 1). The median duration of stay in the NICU was statistically similar in both groups; 25 days (range, 1-90 days) for the immediate delivery group and 30 days (range, 1-130 days) for expectant management group (Table 3). The percentage of ventilation requirement in neonates was similar in both groups (47% vs. 72% respectively) (p=0.08). Composite adverse outcomes for both groups were also similar (p=0.498). Although neonatal mortality was more common in the expectant management group compared with the immediate delivery group (35% vs. 14%, respectively), it did not reach statistical significance (Table 3). Neonatal outcomes were also similar in the subgroups of the expectant management group (Table 4). Two out of 3 neonates born to mothers with chorioamnionitis expired; only one could be discharged from the NICU.

When binary logistic regression analysis with backward stepwise elimination was conducted, gestational age at delivery was found as the only factor related with neonatal composite adverse outcome. The other variables, which were gestational age at admission, latency period, WBCs and CRP at delivery, betamethasone use and birth-weight, were not found as factors related to fetal and maternal morbidity. (Predicted logit of composite adverse outcome=37.266+(-0.162) x gestational age at delivery (Omnibus test of model: p<0.001; Nagelkerke R Square=0.700; Hosmer-Lemeshow goodness of fit test p=0.553).

Discussion

Management of PPROM with regard to gestational age is a challenging issue. Immediate delivery is the preferred method with acceptable outcomes because fetal lung maturity is almost achieved after 34 weeks of gestation. However, if the gestational age is smaller than 32 weeks, the management becomes more complex and difficult. While dealing with these PPROM cases, one should weigh the risks of immediate delivery and expectant management. If immediate delivery is the choice, neonatal complications and mortality related with prematurity of newborn are the main disadvantages. If expectant management is the strategy of choice, the risks of chorioamnionitis and neonatal sepsis are the two arising morbidities. In order to overcome these risks and to have the best neonatal outcomes, we need to increase our knowledge about the optimal expectancy period.

Our study demonstrated that gestational age in PPROM is inversely associated with duration of latency. Patients with a shorter gestational age had a longer latency period until delivery. The antenatal complication rate was found higher with prolongation of pregnancy. However, expectant management in PPROM between 24 and 32 weeks was not associated with increased neonatal morbidity and mortality compared with the immediate delivery group. Gestational age at delivery was the only confounding factor for composite adverse outcomes.

Similar to our study, Aziz et al.[6] demonstrated that gestational age at the time of PPROM was inversely associated with duration of latency. Nevertheless, there was no consensus on length of latency to optimize the neonatal morbidity. Peaceman et al.[7]

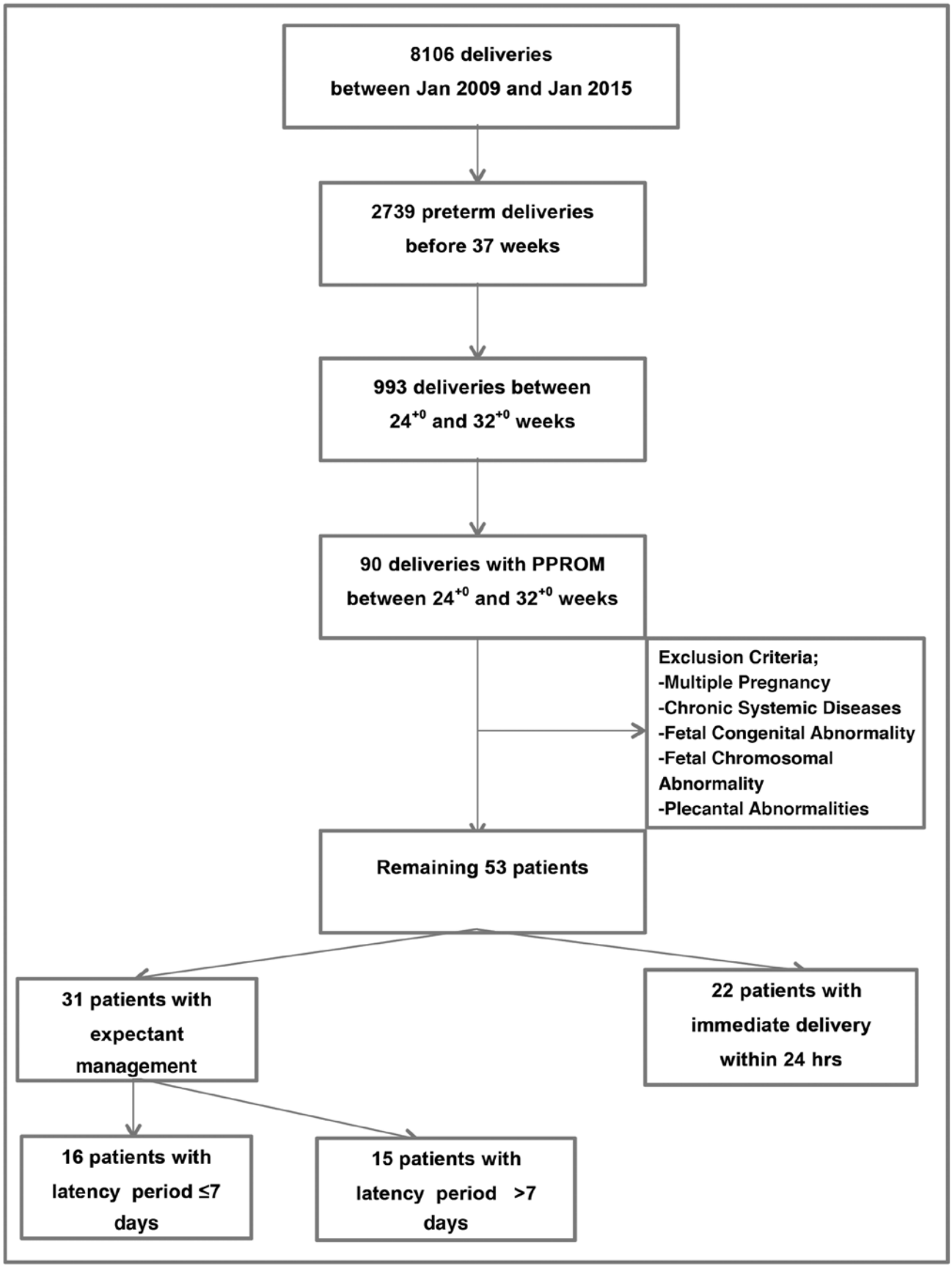

Figure 1. Patient selection flow diagram

assessed the optimal length of latency in patients with PPROM before 32 weeks of gestation in a multicenter randomized study. The authors found that with expectant management, the optimal latency period was approximately 9 days before 28 weeks of gestation, but was significantly shorter in patients with 29-30 weeks of gestation[7]. In another study for all gestational age groups between 24-34 weeks, the best outcomes were in patients with PPROM of 1 to 7 days, and survival was lowest in infants where PPROM was >28 days[8].

Manuck et al.[9] found that in patients with PPROM, infection but not latency was associated with major perinatal morbidity. In another study, it was found that composite neonatal morbidity in neonates born with a latency period >7 days was higher compared with the composite morbidity of neonates born at the same gestational age without PPROM[10]. The reason for the higher rate of adverse neonatal outcomes in cases of uncomplicated PPROM is unclear. One possible explanation may be the presence of subclinical chorioamnionitis, which has been shown to complicate up to 25-40% of cases of PPROM[11]. However, other studies have shown the majority of infants with prolonged latency periods following PPROM did not have increased morbidity and mortality risk in the NICU compared with similar gestational age infants born to mothers with a shorter latency period of PPROM, similar to our results[6,8]. Gestational age was the only confounding factor for composite adverse neonatal outcomes. Thus, we argue that expectant management might be considered as a good alternative in the management of patients with PPROM <32 weeks.

Although there was no statistical difference in gestational age at delivery, the mean birthweight was lower in the expectant management group compared with the immediate delivery group. This may be attributed to the presence of oligohydramnios and inflammatory process in the prolonged latency period. The literature about birthweight is conflicting. Some studies showed that oligohydramnios at admission was associated with adverse neonatal outcomes[12,13]. In contrast, others reported that oligohydramnios was not related with fetal growth restriction[14]. Subclinical chorioamnionitis has also been shown to be responsible for fetal growth restriction[15]. In our study, WBC was not statistically higher in the expectant management group at delivery. CRP level at birth was one of the confounding factors for maternal complications but not in neonatal composite adverse outcomes. It is one of the clinical findings in subclinical chorioamnionitis, which may also explain the presence of lower fetal weight in these patients. Additionally, the shorter gestational age at admission in the expectant management group may be another reason for the lower birthweights compared with the immediate delivery group.

This small-sample-sized retrospective study showed that expectant management may be considered before 32 weeks of gestation in appropriate patients. Optimizing maternal-fetal management with a conservative treatment toward prolonging pregnancy for as long as possible seems pragmatic because antenatal and neonatal complications are all effected by gestational age. We conclude that further randomized and larger trials are required to establish the optimum length of the latency period in this particular condition.

Table 1. Maternal and neonatal characteristics of the patients

	Immediate delivery (n=22)	Expectant management (n=31)	p value
Maternal Characteristics			
Maternal age (years)*	29 (18-37)	30 (21-42)	NS
Gravidity*	2 (1-6)	2 (1-6)	NS
Gestational age at admission (days)*	218 (182-224)	189 (168-224)	<0.05
WBC at admission (n/mm^3)**	14.400±5.3	13.300±4.3	NS
CRP at admission (mg /dL)*	0.9 (0-11)	0.9 (0-7.9)	NS
Gestational age at delivery (days)*	218 (182-224)	207 (176-267)	NS
WBC at delivery (n/mm^3)**	14.500±5.4	15.200±4.4	NS
CRP at delivery (mg /dL)*	0.9 (0-11)	2.26 (0-20)	NS
Latency period (days)*	--	6 (2-8)	--
Antenatal complications***	4 (18%)	15 (48%)	<0.05
Neonatal Characteristics			
Birth weight (grams)**	1.613±452	1.274±429	<0.05
Apgar score at 1st minute*	6 (1-10)	6 (1-9)	NS
Apgar score at 5th minute*	8 (3-10)	8 (4-10)	NS

*Values are given in median (min-max), **Values are given in mean with standard, *** Value is given as number (percentage), WBC: White blood cell, CRP: C-reactive protein, NS: Not significant

Table 2. Comparisons between subgroups of patients with expectant management

	Latency period ≤7 days (n=16)	Latency period >7 days (n=15)	p value
Gestational age at admission*	189 (170-224)	171 (156-224)	NS
Gestational age at delivery*	196 (177-243)	222 (176-267)	NS
Antenatal complications (%)**	9 (56%)	6(40%)	NS
WBC at delivery (n/mm^3)***	16.1±4.5	14.5±4.4	NS
CRP at delivery (mg/L)*	0.9 (0-11)	1.34 (0-20)	NS

*Values are given in median (min-max), **Value given as n (percentage), *** Values are given in mean with standard deviation, WBC: White blood cell, CRP: C-reactive protein, NS: Not significant

Table 3. Comparisons between neonatal outcomes

	Immediate delivery (n=22)	Expectant management (n=31)	p value
Requirement for ventilation*	10 (47%)	21 (72%)	NS
Duration in NICU (days)**	25 (1-90)	26 (1-130)	NS
Composite outcome*	16 (73%)	24 (82%)	NS
Respiratory distress syndrome	13 (59%)	13 (45%)	NS
Intraventricular hemorrhage	4 (19%)	4 (14%)	NS
Retinopathy of prematurity	3 (18%)	3 (17%)	NS
Necrotizing enterocolitis	0	2 (6%)	NS
Sepsis	14 (63%)	24 (82%)	NS
0_2 Necessity at 28th day*	5/18 (27%)	12/22 (54%)	NS
Neonatal mortality*	3 (14%)	11 (35%)	NS

*Values are given as n (percentage), **Value is given in median (min- max), NICU: Neonatal intensive care unit, NS: Not significant

Table 4. Comparisons of neonatal outcomes between subgroups of patients with expectant management

	Latency period ≤7 days (n=16)	Latency period >7 days (n=15)	p value
Requirement for ventilation*	14 (87%)	7/13 (53%)	NS
Duration in NICU (days)**	25 (1-90)	26 (1-130)	NS
Composite outcome*	14 (88%)	10 (76%)	NS
Respiratory distress syndrome	10 (62%)	3 (23%)	NS
Intraventricular hemorrhage	2 (12.5%)	2 (14%)	NS
Retinopathy of prematurity	3 (27%)	0	--
Necrotizing enterocolitis	2 (12,5%)	0	--
Sepsis	14 (87%)	10 (66%)	NS
0_2 necessity on the 28th day *	8/12 (66%)	4/10 (40%)	NS
Neonatal mortality*	5 (31%)	6 (40%)	NS

* Values are given as n (percentage) ** Values are given as median (min-max), NICU: Neonatal intensive care unit, NS: Not significant

Ethics

Ethics Committee Approval: Retrospective work, Informed Consent: Consent form was filled out by all participants.
Peer-review: External peer-reviwed.

Authorship Contributions

Concept: Bilge Çetinkaya Demir, Mehmet Aral Atalay, Design: Mehmet Aral Atalay, Data Collection or Processing: Kiper Aslan, Bilge Çetinkaya Demir, Analysis or Interpretation: Kiper Aslan, Bilge Çeinkaya Demir, Literature Search: Kiper Aslan, Bilge Çetinkaya Demir, Writing: Bilge Çetinkaya Demir, Kiper Aslan, Mehmet Aral Atalay.
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Vitamin D deficiency in pregnancy is not associated with diabetes mellitus development in pregnant women at low risk for gestational diabetes

Gestasyonel diyabet açısından düşük risk taşıyan gebelerde D vitamini eksikliği ile diyabet gelişimi arasında bağlantı yoktur

Mehmet Bal, Gülçin Şahin Ersoy, Ömer Demirtaş, Sefa Kurt, Abdullah Taşyurt

Tepecik Education and Research Hospital, Department of Obstetrics and Gynecology, İzmir, Turkey

Abstract

Objective: We aimed to investigate the effect of vitamin D deficiency as a risk factor for the development of gestational diabetes mellitus (GDM) among pregnant women without known risk factors.

Materials and Methods: The study was conducted on pregnant women who had been under regular follow-up and had low risk for GDM development. The patients were divided into two groups according to the presence of GDM; GDM and no GDM (control) group. Body mass index (BMI), sociodemographic data including level of education and nutritional habits were recorded. Serum 25 (OH) vitamin D_3 levels, hemoglobin, hematocrit, and mean corpuscular volume (MCV) values were measured. An oral glucose tolerance test was performed, between 24 and 28 weeks of pregnancy.

Results: GDM ratio was calculated as 4.6%. The false positive rate of 50 g oral glucose load screening test was found to be 16.5%. The BMI levels of women diagnosed as having GDM and those with no GDM group at the beginningof the pregnancy period were calculated as 24.3±2.6 and 22.8±1.6 kg/m^2 respectively, exhibiting a statistically significant difference between the two groups (p=0.001). Hemoglobin, hematocrit, and MCV values did not show a statistically significant difference between the two groups (p>0.05). The levels of 25 (OH) vitamin D_3 of the study groups were found comparable in both groups (p=0.13).

Conclusion: Plasma levels of vitamin D may not be a contributing factor for the development of GDM in women with a low risk for GDM.

Keywords: Gestational diabetes mellitus, 25 (OH) vitamin D_3, vitamin D deficiency

Öz

Amaç: Gestasyonel diabetes mellitus (GDM) için bilinen risk faktörü bulunmayan gebelerde maternal plazma D vitamini eksikliğinin GDM açısından risk faktörü olup olmadığını araştırmaktır.

Gereç ve Yöntemler: GDM açısından düşük riskli olup düzenli poliklinik takiplerine gelen gebeler çalışmaya dahil edildi. GDM tanısı alan ve almayan olarak iki gruba ayrılan hastaların vücut kitle indeksi (VKİ) değerleri, sosyodemografik verileri, beslenme alışkanlıkları kaydedildi. Hemoglobin, hematokrit ve ortalama eritrosit hacim (MCV) değerleri ölçüldü. Yirmi dördüncü ve yirmi sekizinci gebelik haftasında oral glukoz yükleme testi yapıldı ve serum 25 (OH) vitamin D_3 seviyeleri karşılaştırıldı.

Bulgular: Çalışma grubumuzda GDM sıklığı %4,6 bulundu. 50 gr tarama testinin yalancı pozitiflik oranını %16,5 olarak saptandı. Gebelik başlangıcındaki VKİ değerleri GDM tanısı alan hastalarımızda 24,3±2,6 kg/m^2 iken, kontrol grubundaki gebelerde 22,8±1,6 kg/m^2 tespit edildi (p=0,001). Hemoglobin, hemotokrit ve MCV değerleri kontrol ve GDM gruplarında anlamlı farklılık göstermemiştir (p>0,05). GDM grubu ve kontrol grubunda hastaların 25 (OH) vitamin D_3 sırasıyla 28,5±11,6 ve 25,4±9,3 bulunmuştur (p=0,13).

Sonuç: Gebelik fizyolojisi normal insan fizyolojisinden farklı olduğu için ve gebelik hormonlarıyla birlikte gebeliğin fizyolojik gelişimi sürecinde insülin rezistansını etkileyecek çok faktör vardır. Çalışmamızda D vitamini düzeyi ile insulin rezistansı ve GDM gelişimi arasında herhangi bir ilişki bulunamamıştır.

Anahtar Kelimeler: Gestasyonel diabetes mellitus, 25 (OH) vitamin D_3, D vitamini eksikliği

Address for Correspondence/Yazışma Adresi: Gülçin Şahin Ersoy, MD,
Tepecik Education and Research Hospital, Department of Obstetrics and Gynecology, İzmir, Turkey
Phone: +90 506 680 94 94 **E-mail:** gulcinsahinmd@gmail.com
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PRECIS: We evaluated the effect of vitamin D deficiency as a contributing factor for the development of gestational diabetes among pregnant women who have a low risk for gestational diabetes

Introduction

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance that appears after 24 weeks of gestation[1,2]. There is increasing evidence that vitamin D, a secosteroid synthesized in the skin, plays a vital role in the maintenance of normal glucose balance. 1, 25-dihydroxy vitamin D_3 is responsible for the increase of the production and secretion of insulin and for the concurrent decrease of insulin resistance[3,4].

The high prevalence of vitamin D deficiency among pregnant women is a well established. However, scientific data regarding the correlation of vitamin D with glucose balance during pregnancy and the occurrence of GDM is still insufficient and inconsistent[5]. In this study, we aimed to determine whether vitamin D levels in maternal plasma were a risk factor for the development of GDM among pregnant women who had no other known risk factors for GDM.

Materials and methods

This cross-sectional study was conducted on pregnant women in the first trimester who were receiving antenatal care in the Aegean Obstetrics and Gynecology Education and Research Hospital in İzmir, Turkey. The study was approved by the local ethics committee of the hospital, and written consent was given by each patient. All subjects had low risk for GDM development without any other accompanying medical condition. We accepted the risk factors for GDM development as those determined by the American Diabetes Association (ADA) and the American Congress of Obstetricians and Gynecologists (ACOG)[6,7]. Therefore, women with obesity, aged more than 35 years, with prior history of gestational diabetes mellitus in a previous pregnancy, and family history of diabetes mellitus were excluded. The inclusion criteria for the study were pregnant women aged between 15 and 35 years; a negative C-reactive protein value; the absence of accompanying illness that could interfere with the interpretation of diabetes (e.g. Cushing's syndrome, acromegaly); a medical history devoid of alcohol consumption; diabetogenic agent use (e.g. steroids); multiple pregnancy; hematological illness; and the absence of glucose in urine analysis.

One thousand four hundred pregnant women with a low risk of gestational diabetes who applied to our clinic in the first trimester of pregnancy were enrolled in the study. Sociodemographic variables, hemoglobin, hematocrit, and mean corpuscular volume (MCV) levels were all recorded. A 50-g oral glucose load screening test was conducted between the 24th and 28th weeks of gestation. In accordance with the guidelines recommended by the ACOG, the two-stage approach was used for the screening and diagnosis of GDM. All pregnant women with a low risk for GDM ingested a solution containing 50 g of sugar and venous blood samples were collected one hour later; patients whose plasma glucose levels were above 140 mg/dL were considered as abnormal. Those with abnormal results underwent a 100-g oral glucose tolerance test (OGTT) approximately 2 weeks later. Women who matched at least two of the criteria listed below were diagnosed as having GDM:

Fasting blood glucose level ≥95 mg/dL (5.3 Mmol/L),
Blood glucose level at the 1st hour ≥180 mg/dL (10 Mmol/L),
Blood glucose level at the 2nd hour ≥155 mg/dL (8.6 Mmol/L),
Blood glucose level at the 3rd hour ≥140 mg/dL (7.8 Mmol/L).

Of the 1322 patients with normal test results, 50 women were randomly selected as the control group using a simple computerized randomization chart generator. Seventy-eight patients with abnormal test results proceeded with the 100-g OGTT and 65 pregnant women were diagnosed as having GDM. Fifteen patients who did not comply with the regular follow-ups, who had an obstetric complication, and those who declared their intention to leave the research protocol were excluded from the study. Following the OGTT examination, 25 (OH) vitamin D_3 levels were measured and recorded for each patient, which is accepted as the most dependable form of vitamin D in reflecting the actual level of vitamin D in the body. All blood sampling was undertaken in the summer season because vitamin D levels show seasonal variation. In both groups, the measurement of serum 25 (OH) vitamin D_3 levels was performed using liquid-liquid extraction with a liquid UPLC/MS/MS chromatography-tandem mass spectrometer (manufacturer required). The lowest level of 25 (OH) vitamin D_3 without any change in serum PTH levels is 30 ng/mL, thus this was accepted as the lower limit for vitamin D adequacy[8-10]. Levels between 20 and 30 ng/mL were designated as borderline deficiency, and below 20 ng/mL was overt deficiency.

Statistical Analysis

The arithmetic mean, standard deviation, frequency and ratio values were used for the descriptive statistical analysis of the data. The distribution of data was checked using the Kolmogorov-Simirnov test. Normally distributed data were analyzed using the independent sample t-test, data without normal distribution were evaluated using the Mann-Whitney U test. Nominal data were analyzed using the Chi-square test.

Results

Following the 100-g OGTT, 65 out of the 78 pregnant women with an abnormal 50-g glucose screening test were diagnosed as having GDM as per the ACOG criteria (the false positive rate of the 50-g OGT was found 16.5%). The GDM ratio was calculated as 4.6%. Fifty of the 65 pregnant women with GDM met the inclusion criteria. The BMI of the women who were diagnosed

as having GDM was calculated as 24.3, whereas it was 22.8 in the control group; there was a statistically significant difference between the two groups (p=0.001). The demographic features of both groups are summarized in Table 1.

The levels of hemoglobin, hemotocrit, and MCV were similar in both groups (p>0.05). The level of 25 (OH) vitamin D_3 in patients did not exhibit a statistically significant difference between the two groups (p=0.13). Moreover, the comparison of fish and milk consumption as well as the rate of vitamin pills use did not reveal a statistically significant difference between the groups (p>0.05) (Table 1). In addition, our study population lived in a sunny region and all patients had normal sun exposure frequency (≥ 3day/week and ≥30 minutes/day) and none were wearing strict religious clothing.

Discussion

The aim of the study was to investigate the association between vitamin D deficiency and GDM development in pregnant women at low risk for GDM. Our results showed that vitamin D levels were not associated with the development of GDM. To the best of our knowledge, this is the first study to evaluate the effects of vitamin D levels on the development of GDM in pregnant women at low risk for GDM.

Table 1. Patient characteristics and 25 (OH) vitamin D_3 levels

	GDM (n=50)	Control (n=50)	p value
Age, years	30.9±3.5	26.3±4.4	0.001
Gravidity, median	2	2	NS
BMI, kg/m^2	24.3±2.6	22.8±1.6	0.001
Education			
Pimary and secondary school	33 (66%)	41 (82%)	NS
High school	14 (28%)	6 (12%)	
University	3 (6%)	3 (6%)	
Nutrition			
One cup of milk daily	33 (66%)	41(82%)	NS
Fish consumption (twice a week)	7 (14%)	10 (20%)	NS
Use of multivitamin pill	47 (94%)	47 (94%)	NS
Hemoglobin (g/dL)	11.9±1.3	11.7±1.2	NS
Hemotocrit (%)	34.4±3.6	34±3.2	NS
MCV (fL)	89.0±5.4	87.7±7.2	NS
25 (OH) Vitamin D_3 (ng/mL)	28.5±11.6	25.4±9.3	NS
Groups according to 25 (OH)			
Vitamin D_3 levels			
>30 ng/mL (normal)	25 (50%)	16 (32%)	NS
20-30 ng/mL (moderate deficiency)	10 (20%)	18 (36%)	NS
<20 ng/mL (severe deficiency)	15 (30%)	16 (32%)	NS

Data are presented as mean ± SD or n (%), GDM: Gestational diabetes mellitus, BMI: Body mass index; MCV: Mean corpuscular volume; NS: Non-significant, SD: Standard devitation

GDM is defined as the intolerance for carbohydrates starting from the 24th week of gestation[1,2]. Factors that cause insulin resistance have always attracted the attention of scientists; the recent discovery of the interrelations between vitamin D and the cardiovascular system, immunomodulation, metabolic syndrome, autoimmunity and certain carcinomas has enhanced the popularity of vitamin D. Some studies detected that pancreatic β cells express a vitamin D receptor, and allelic variations in genes involved in vitamin D metabolism suggested a role for 25 (OH) vitamin D_3 in the regulation of insulin secretion and glucose intolerance[11]. In addition, it has been shown that vitamin D deficiency in experimental animals impaired insulin release and glucose tolerance[12,13]. Although deficiency of 25 (OH) vitamin D_3 levels has long been suspected as a risk factor for insulin resistance in GDM pregnancies, the association of vitamin D and GDM is still controversial. Similarly, it has been reported that increased serum iron levels might be related to GDM risk in pregnant women[14,15]. Also, a study conducted by Afkhami-Ardekani and Rashidi[16] showed that women with GDM had significantly higher levels of serum ferritin, iron, hemoglobin and MCV. In order to evaluate this factor, we also examined the MCV value, which is a robust index of iron status in pregnant women[17]. The comparison of the MCV levels revealed no statistically significant difference between groups.

The ADA reported the prevalence of GDM in pregnant women as 4%[6]. In Turkey, the prevalence of GDM varies between 3-8%[18]. In the present study, the GDM ratio was found as 4.6%; however, all women in the study were at low risk for GDM development, thus the GDM ratio in this study does not reflect the actual incidence of GDM in Turkey.

Several previous studies demonstrated results consistent with our findings; Flood-Nichols et al.[19], Makgoba et al.,[20] Farrant et al.,[21] and Park et al.,[22] reported no association in the United States of America, the United Kingdom, India, and Korea between vitamin D deficiency and development of GDM. However, Lacroix found that maternal vitamin D deficiency was a risk factor for developing GDM in pregnant women in Canada[23]. These studies did not evaluate the effect of vitamin D deficiency in pregnant women who were at lower risk for developing GDM. Therefore, in the studies that found a higher correlation between vitamin D deficiency and GDM, the results may have been related with other predisposing factors such as older maternal age and prior history of gestational diabetes in a previous pregnancy. In our study, these factors were excluded, thus we suggest that lower vitamin D levels had no association with development of GDM in Turkish pregnant women at low risk for gestational diabetes. Even though there is no consensus about the prophylactic vitamin D treatment for the prevention of developing GDM in higher risk women, vitamin D supplementation is essential for pregnant

women in terms of its potentially beneficial effects. It is known that vitamin D supplementation therapy reduces the incidence of preterm labor, gestational diabetes, and small-for-gestational-age babies[24]. There are some limitations of the study; first, the sample size was rather small because it had been designed as a prospective study. The total number of pregnant women was 1400 but only 65 developed GDM; this low ratio of GDM (+) women in the study group was thought to be caused by the inclusion of women with lower risk of GDM to the study. Secondly, we did not measure vitamin D levels in the first trimester; therefore, the influence of the variation in vitamin D levels was not evaluated.

Conclusion

The physiologic properties of the pregnancy period differ from normal female physiology and there are many factors such as pregnancy hormones that act on the emergence of insulin resistance during the physiologic development of pregnancy. Therefore, we were unable to find a direct correlation between vitamin D levels and GDM development as documented in several previous studies. New and long-term prospective studies in a broader patient series including pregnant women are needed to further clarify the precise relationship between vitamin D and GDM.

Ethics

Ethics Committee Approval: The study was approved by the Local Ethics Committee of Tepecik Education and Research Hospital, Informed Consent: A consent form was filled out by all participants., Peer-review: External peer-reviewed.

Authorship Contributions

Concept: Mehmet Bal, Sefa Kurt, Abdullah Taşyurt, Design: Mehmet Bal, Gülçin Şahin Ersoy, Ömer Demirtaş, Data Collection or Processing: Mehmet Bal, Analysis or Interpretation: Mehmet Bal, Gülçin Şahin Ersoy, Ömer Demirtaş, Literature Search: Mehmet Bal, Gülçin Şahin Ersoy, Writing: Gülçin Şahin Ersoy, Ömer Demirtaş.
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Conventional 22- and 20-gauge needle for second trimester amniocentesis: A comparison of short term outcomes

Konvansiyonel 22- ve 20-gauge iğneleriyle yapılan amniyosentez işlemlerinin kısa dönem sonuçlarının karşılaştırılması

Seyit Ali Köse, Mehmet Özgür Akkurt, And Yavuz, Serenat Eriş, Esra Nur Tola, Mehmet Okan Özkaya, Mekin Sezik

Süleyman Demirel University Faculty of Medicine, Department of Obstetrics and Gynecology, Isparta, Turkey

Abstract

Objective: To compare the short-term outcomes of two different-sized needles for genetic amniocentesis.
Materials and Methods: A total of 271 amniocentesis were retrospectively evaluated in 2 groups concerning the size of the needles used during the procedure: Conventional 20-gauge (G) (n=164) and 22G (n=107). Periprocedural complications and cost-effectiveness were compared across the groups.
Results: There were no differences between groups concerning complications within 15 days after the procedure (fetal loss, 0.6% versus 0.9%, and amniotic fluid leak 1.2% versus 1.8%, p=0.99 for each). The 22G needle was significantly more cost efficient (p<0.0001).
Conclusion: The 22 G spinal needle is convenient for second trimester amniocentesis with similar complication rate and has a favorable cost profile.
Keywords: Amniocentesis, complication, cost-effectiveness, needle size

Öz

Amaç: Farklı boyutlardaki iki amniyosentez iğnesinin kısa dönem sonuçlarının karşılaştırılmasıdır.
Gereç ve Yöntemler: Amniyosentez işlemi uygulanan 271 gebe kadın retrospektif olarak incelendi. Kullanılan iğnenin boyutuna göre kadınlar, konvansiyonel 20 gauge (G) amniyosentez iğnesi (n=164) ve 22 G spinal iğnesi (n=107) ile işlem yapılanlar olarak iki gruba ayrıldı. Gruplar işleme bağlı komplikasyon ve maliyet açısından karşılaştırıldı.
Bulgular: Gruplar arasında 15 gün içinde prosedüre bağlı komplikasyon açısından fark yoktu (fetal kayıp; grup 1'de %6, grup 2'de %0,9, amniyotik mayi sızıntısı; grup 1'de %1,2, grup 2'de %1,8, her iki grupta p=1). 22 G iğnenin maliyeti anlamlı olarak daha uygundu (p<0,0001).
Sonuç: 22 G spinal iğne ikinci trimester amniyosentezinde benzer komplikasyon oranlarına sahipken maliyet etkinliği açısından daha uygundur.
Anahtar Kelimeler: Amniyosentez, komplikasyon, uygun maliyet, iğne boyutu

Introduction

Amniocentesis is an invasive procedure. Thousands of amniocentesis procedures have been performed for prenatal karyotyping since its first use in 1966[1]. Procedure-related complications both during and after amniocentesis have been particularly well-defined, these include amniotic fluid leakage, rupture of chorioamniotic membranes, direct or indirect fetal trauma, infection, and fetal loss, the latter two being the most common complications[2,3].

No single needle type used during amniocentesis has been reported to be associated with lower complication rates[3]. Some investigations have compared various needle sizes, periprocedural local anesthetic use, and different techniques of needle use. However, these revealed similar complication rates, especially when different needle sizes were used. Lower procedure-related morbidity seems to be associated with proper selection of pregnancies for the invasive procedure and the experience of the operator performing the amniocentesis[4].

During the present study, we obtained data on a considerable number of amniocentesis procedures concerning different needle sizes in a tertiary perinatology unit. Our aim in this observational study was to compare the complications (including fetal loss, vaginal bleeding, pain, maternal fever, and amniotic fluid leakage), efficacy, and cost effectiveness of two needle sizes used by three professionals for amniocentesis procedures.

Address for Correspondence/Yazışma Adresi: Mehmet Özgür Akkurt, MD,
Süleyman Demirel University Faculty of Medicine, Department of Obstetrics and Gynecology, Isparta, Turkey
Phone: +90 505 631 31 15 **E-mail:** mozgurakkurt@gmail.com
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Materials and Methods

This observational study was carried out at the Perinatology Unit, Faculty of Medicine, Süleyman Demirel University between January 2012 and December 2014. The study groups included women aged between 24 and 37 years. Two hundred seventy-one pregnant women scheduled for genetic amniocentesis were retrospectively evaluated in the two groups according to the size of the needle used for amniocentesis. Amniocentesis procedures were performed either with a 20-gauge (G) needle specific for amniocentesis and chorion villus sampling (Egemen International Amniocentesis Needle, İzmir, Turkey) (group 1), or with a 22 G spinal needle (Zhejiang Fert Medical Device Co., Ltd. China) (group 2). The participant's characteristics such as maternal age, parity, and gravidity were recorded. All procedures were conducted in accordance with the Helsinki Declaration. The study protocol was subject to local ethics committee approval. Written informed consent was obtained from all patients who participated in this study.

All women in both arms of the study underwent the standard of care technique under transabdominal sonographic guidance with free hand insertion of the needle into the amniotic cavity[3-14]. Approximately 1 mL/gestation week of amniotic fluid was aspirated. Data recorded included maternal age, gravidity, parity, history of maternal surgery and the direct cost of the needle used during the procedure. Fetal heart activity was recorded with Doppler ultrasound before and after the procedure. Women were followed up for the development of any complications including vaginal or needle site amniotic fluid leakage, vaginal bleeding, fetal loss, maternal fever, and pain during a 15-day period following the procedure.

Statistical analyses were performed using SPSS version 16.0 software (SPSS Chicago, Il., USA). Student's t-test, Chi-square contingency table analyses, and Fisher's exact test were used for comparisons of variables across the groups, with statistical significance set at $p<0.05$.

Results

Table 1 lists the demographic characteristics of women participating in the study. A total of 271 women who underwent amniocentesis in our unit over the 3-year period were included. All women had a singleton pregnancy. Indications for amniocentesis were as follows: increased risk for first and second trimester screening test, advanced maternal age, and family history of genetic disorders. The mean gestational age during the procedure was 17.8±0.9 standard deviation weeks for the whole study group. There were no significant differences between the groups concerning maternal age, parity, and gestational age at intervention (Table 1). The complication rates of the operators (n=3) were also similar ($p>0.05$). Abnormal karyotypes were found in 5.8% of the total sample with trisomy 21 being the most commonly detected aberrance. The distribution of abnormal karyotypes did not differ among the two groups ($p>0.05$).

The number of needle puncture attempts and the volume of collected amniotic fluid did not differ among the two groups. Pain during and/or after the procedure was reported by 10 women (6.1%, group 1) and 9 women (8.4%, group 2), respectively ($p=0.627$). Amniotic fluid leakage was observed in 4 women, 2 in each group. There was no significant difference between the groups according to maternal fever and vaginal bleeding. A total of 2 fetal losses occurred within 2 weeks of amniocenteses (1 in each group). Therefore, complication rates were similar (Table 2). However, cost

Table 1. The demographic data of the pregnant women in study group

	Group 1 (n=164) 20-G needle	Group 2 (n=107) 22-G spinal needle	p value
Age (years)	31.2±6.3 (24-39)	31.5±6.2 (25-41)	0.629
Gravidity	1.7±0.7 (2-4)	2.2±0.9 (2-5)	0.010
Parity	0.7±0.7	0.8±0.7	0.209
Previous maternal surgery[a]	17 (10.3%)	11 (10.2%)	0.982

G: Gauge, [a]: abdominal and/or pelvic, Data are given as mean ± standard deviation (range within parentheses) or frequency (percentages within parentheses)

Table 2. Complications during and after the procedures*

	Group 1 (n=164) 20-G needle	Group 2 (n=107) 22-G needle	p value
Pain during and/or after the procedure	10 (6%)	9 (8.4%)	0.627
Amniotic fluid leakage	2 (1.2%)	2 (1.8%)	0.99
Maternal fever	36.4±0.5	36.5±0.6	0.99
Fetal loss	1 (0.6%)	1 (0.9%)	0.99
Vaginal bleeding	1 (0.6%)	1 (0.9%)	0.99
Requirement for multiple needle puncture (%)	5 (3.0%)	3 (2.8%)	0.99
Amount of amniotic fluid collected (mL)	15.8±5.6	16.4±6.3	0.143

Data are given as frequency (percentages within parentheses) * within 15 days follow-up, G: Gauge

was significantly lower with the 22 G spinal needle (14 USD for 20G needle versus 0.53 USD for 22 G needle, p<0.0001).

Discussion

Patient comfort and safety as well as cost effectiveness are important issues for amniocentesis. Cost-effectiveness might be a concern because the procedure is performed quite frequently and laboratory cost for karyotyping is relatively high. Therefore, needle size, length, and ultrasonographic visibility would be expected to have an effect on quality, comfort, and cost-effectiveness of this invasive procedure. Although use of needles with lower sizes were considered to be associated with less trauma and complications, previous studies did not support such theoretical statements; no extra advantage was provided with different-size needles[2,7].

Previous investigations have included comparisons of various needle sizes, needles with improved ultrasound visibility characteristics, and simple large-bore spinal needles[2,5]. However, cost effectiveness for different needle sizes has not been investigated. In the current study, we expanded previous data by including cost effectiveness in our design.

Previous publications compared various parameters including post-procedure complications among needles of different sizes used during amniocentesis. These previous data revealed that different needles were generally comparable with no significant differences concerning morbidity[2,6,7]. Small-sized needles have been associated with certain difficulties during the procedure. These include longer amniotic fluid aspiration times, primarily due to clogging and requirement for a second administration[8]. Our clinical experience with the 22 G spinal needle was somewhat similar, indicating longer aspiration time, clogging due to particulation, and requirement for further punctures; however, the retrospective design of our study did not allow for measurements of the exact aspiration time. Devlieger et al.[9] reported similar mean duration of sampling among all operators. However, when experience was considered, expert operators showed shorter sampling times with a 22 G versus 23 G needle.

One of the most devastating complications of amniocentesis is fetal loss. Recent data have indicated experience as the most important factor in effecting fetal loss[10,11]. Large-bore needles might be associated with relatively easier puncture and fluid aspiration as well as shorter interval and can facilitate procedures that require transplacental passage[12]. One would expect large-bore needles to lead to increased intrauterine bleeding following transplacental passage[11,13]. However, this is not supported by at least one study that reported more intrauterine (intra-amniotic) bleeding with needles of smaller size[2]. Moreover, investigations that included very small-gauged needles such as 29 G reported difficulties during myometrial passage and membrane puncture as the primary drawback[8,14]. Although there are some data on the cost effectiveness of karyotype analysis, needle costs have not been included in previous studies[12]. Proper indication, informed consent, and experienced operator decrease fetal loss rates of amniocentesis procedures[10]. Single amniotic entry and decreased procedure time also decrease maternal anxiety.

Conclusion

The exception of cost, our data from a single center revealed similar outcomes with needles of two different sizes used during amniocentesis procedures by theree different operators. Therefore, 22 G needles, which are commonly used during spinal anesthetic administration, may also be suitable for performing amniocenteses.

Ethics

Ethics Committee Approval: The hospital ethics committee, Informed Consent, has approved working for Süleyman Demirel University Faculty of Medicine: Written in formed consent was obtained from all partici pants.

Peer-review: External and Internal peer-reviewed.

Authorship Contribtions

Surgical and Medical Practices: Mekin Sezik, Mehmet Okan Özkaya, Concept: Seyit Ali Köse, Design Data Collection or Processing: And Yavuz, Serenat Eriş Yalçın, Analysis or Interpretation: Mekin Sezik, Literature Search: Seyit Ali Köse, Mehmet Özgür Akkurt, Writing: Esra Nur Tola, Seyit Ali Köse, Mehmet Özgür Akkurt, Mekin Sezik.

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Prevalence of endometrial polyps coexisting with uterine fibroids and associated factors

Uterin fibroid olgularında endometrial polip prevalansı ve ilişkili faktörler

Tuğba Kınay[1], Zehra Öztürk Başarır[2], Serap Fırtına Tuncer[1], Funda Akpınar[1], Fulya Kayıkçıoğlu[1], Sevgi Koç[1]

[1]*Etlik Zübeyde Hanım Women's Health Training and Research Hospital, Clinic of Obstetrics and Gynecology, Ankara, Turkey*

[2]*Zekai Tahir Burak Women's Health Training and Research Hospital, Clinic of Obstetrics and Gynecology, Ankara, Turkey*

Abstract

Objective: The aim of the study was to investigate the prevalence of endometrial polyps in patients with uterine fibroids and associated factors of coexistence of these two pathologies.

Materials and Methods: The medical records of 772 patients who underwent hysterectomy because of uterine fibroids were retrospectively reviewed. Patients were divided into two groups according to the presence of endometrial polyps in the histopathologic examination. Demographic, clinical and histopathologic findings of the patients with and without endometrial polyps were compared. Student's t-test, Mann-Whitney U test, Pearson's Chi-square test, and logistic regression analysis were used for statistical analysis.

Results: The prevalence of the endometrial polyps in uterine fibroid cases was found 20.1% (n=155). Age ≥45 years (odds ratio [OR] 1.61; 95% confidence interval [CI]: [1.06-2.44]; p=0.014), presence of hypertension (23.9% vs. 17.5%; p=0.047), endometrial hyperplasia (OR 4.00; 95% CI: [1.92-8.33]; p<0.001) and cervical polyps (OR 3.13; 95% CI: [1.69-5.88]; p<0.001) were significantly associated with the coexistence of endometrial polyps and uterine fibroids. Endometrial polyps were more common in patients with ≥2 fibroids (p=0.023) and largest fibroid <8 cm (p=0.009). A negative correlation was found between condom use and endometrial polyps (8.1% vs. 3.9%; p=0.044).

Conclusions: The prevalence of the endometrial polyps coexisting with uterine fibroids was 20.1%. Age, hypertension, endometrial hyperplasia, cervical polyps, and number of fibroids were positively correlated; condom use and size of largest fibroid were negatively correlated with the coexistence of these two pathologies.

Keywords: Cervical polyps, condom, endometrial hyperplasia, endometrial polyps, uterine fibroids

Öz

Amaç: Çalışmanın amacı uterin fibroid olgularında bulunan endometrial polip prevalansını ve bu iki patolojinin birlikteliği ile ilişkili faktörleri araştırmaktı.

Gereç ve Yöntemler: Uterin fibroid tanısı ile histerektomi yapılan 772 hastanın tıbbi kayıtları retrospektif olarak incelendi. Hastalar, histopatolojik incelemede endometrial polip varlığına göre iki gruba ayrıldı. Grupların demografik, klinik ve histopatolojik bulguları karşılaştırıldı. İstatistik analizinde Student's t testi, Mann Whitney U testi, Pearson Ki-kare testi ve lojistik regresyon analizi kullanıldı.

Bulgular: Uterin fibroid olgularında endometrial polip prevalansı %20,1 (n=155) bulundu. Yaş ≥45 (göreceli olasılıklar oranı [OR] 1,61; %95 güven aralığı (CI): [1,06-2,44]; p=0,014), hipertansiyon (%23,9 vs. %17,5; p=0,047), endometrial hiperplazi (OR 4,00; %95 CI: [1,92-8,33]; p<0,001) ve servikal polip varlığı (OR 3,13; %95 CI: [1,69-5,88]; p<0,001) endometrial polip ve uterin fibroid birlikteliği ile ilişkili idi. İki ve daha fazla fibroid varlığında (p=0,023) ve en büyük fibroid boyutu 8 cm'den küçük olan olgularda (p=0,009) endometrial polip daha sık saptandı. Kondom kullanımı ve endometrial polip varlığı arasında ise ters ilişki bulundu (%8,1 vs. %3,9; p=0,044).

Sonuç: Uterin fibroid ile birlikte bulunan endometrial polip prevalansı %20,1 idi. Yaş, hipertansiyon, endometrial hiperplazi, servikal polip ve fibroid sayısı ile bu iki patolojinin birlikteliği arasında pozitif ilişki; kondom kullanımı ve en büyük fibroidin boyutu ile bu birliktelik arasında negatif ilişki mevcuttu.

Anahtar Kelimeler: Servikal polip, kondom, endometrial hiperplazi, endometrial polip, uterin fibroid

Address for Correspondence/Yazışma Adresi: Tuğba Kınay, MD,
Etlik Zübeyde Hanım Women's Health Training and Research Hospital, Clinic of Obstetrics and Gynecology, Ankara, Turkey
Phone: +90 537 847 06 24 **E-mail:** tkinay@hotmail.com

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PRECIS: We investigated the prevalence of the endometrial polyps in patients with uterine fibroids and associated factors with the coexistence of these two pathologies.

Introduction

Endometrial polyps and uterine fibroids are common causes of abnormal uterine bleeding and may coexist. Overgrowth of endometrial glands and stroma leads to endometrial polyps. The prevalence of endometrial polyps is 10-40% in women with abnormal uterine bleeding, and increases with age[1,2]. Transvaginal sonography, saline infusion sonohysterography, and hysteroscopy are the diagnostic tools for endometrial polyps[3,4]. Malignant tissue changes occur in 3.1% of endometrial polyps[1]. Therefore, histopathologic examination of polyps is necessary to exclude malignancy[5,6].

Uterine fibroids are the most common benign tumors in women. Abnormal uterine bleeding occurs in 30% of women with fibroids[7]. Uterine fibroids are the leading causes of hysterectomy, and hysterectomy is the most effective treatment method for symptomatic fibroids in perimenopausal women[8,9]. However, alternative treatments such as progestogens, levonorgestrel-releasing intrauterine system, tranexamic acid, nonsteroidal anti-inflammatory drugs, gonadotropin-releasing hormone analogs, myomectomy, and uterine artery embolization are also available in the management of uterine fibroids[9].

As far as we know, no studies have investigated the coexistence of endometrial polyps and uterine fibroids in the literature. The aim of the retrospective study was to identify the prevalence of the endometrial polyps coexisting with uterine fibroids and associated factors of the coexistence of the two pathologies. Knowledge of the coexistence of these pathologies may help to choose the appropriate therapeutic management. Medical management, myomectomy, or uterine artery embolization are not appropriate treatment options in the presence of malignant endometrial polyps, and hysteroscopic resection alone of endometrial polyps may not be sufficient to relieve abnormal uterine bleeding symptoms in patients with multiple and large uterine fibroids.

Materials and Methods

Women who underwent hysterectomy due to uterine fibroid at a training and research hospital in Turkey, between January 2009 and December 2013, were included the retrospective study. Data were collected from medical records. The study was approved by the institutional review board and written informed consent was obtained from all participants. Exclusion criteria were hysterectomy because of gynecologic malignancy, benign ovarian neoplasm, and uterine prolapse. Patients who underwent myomectomy were also excluded.

Uterine fibroids were diagnosed using preoperative transvaginal ultrasonography, and confirmed through histopathologic examination of hysterectomy specimens, and endometrial polyps were diagnosed through histopathologic examination of the preoperative endometrial biopsy or hysterectomy specimens. Premenopausal patients with a history of abnormal uterine bleeding, and postmenopausal patients with bleeding symptoms and/or endometrial thickness ≥5 mm in ultrasonographic examination underwent preoperative endometrial biopsy. The women were divided into two groups: the study group consisted of women with endometrial polyps and uterine fibroids; and the control group comprised women with uterine fibroids alone. Women's age, body mass index, gravidity, parity, menopausal status, contraception methods, preoperative hemoglobin levels, history of cesarean section, smoking, hypertension, diabetes mellitus, and abnormal uterine bleeding were compared between the two groups.

Heavy menstrual bleeding, intermenstrual bleeding, and postmenopausal bleeding were defined as abnormal uterine bleeding. Regular or irregular bleeding >7 days and/or >80 mL were considered heavy menstrual bleeding. Spotting or more bleeding among regular menses was considered intermenstrual bleeding. The number of uterine fibroids, size and location of the largest fibroid, and other accompanying gynecologic proliferative pathologies (adenomyosis, endometrial hyperplasia, cervical polyps, and endometriosis) were recorded from the womens' histopathology reports.

Statistical analysis was performed usig Statistical Package for Social Science version 15.0 (SPSS Inc., Chicago, IL, USA) software. The normality for continuous variables was checked by using Kolmogorov-Smirnov test. Descriptive statistics are presented as mean ± standard deviation or median (minimum-maximum). Case numbers and percentages are given for categorical variables. Student's t-test or Mann-Whitney U test were used for the comparison of continuous data. Pearson's Chi-square test was used to examine the differences between groups for categorical variables. The odds ratio (OR) of endometrial polyps coexisting with uterine fibroids and 95% confidence interval (CI) were calculated using logistic regression analysis. Statistical significance was accepted as $p<0.05$.

Results

A total of 772 women were analyzed: 155 women with endometrial polyps and uterine fibroids, and 617 women with uterine fibroids alone. The prevalence of endometrial polyps in women with uterine fibroid was 20.1%. The demographic and clinical characteristics of women and contraception methods used are shown in Table 1. Increased age was found as a risk factor for endometrial polyps coexisting with uterine fibroids. The endometrial polyp rate was significantly higher in women aged ≥45 years (OR 1.61; 95% CI: [1.06-2.44]). Hypertension was more common (23.9% vs. 17.5%; p=0.047) in women with endometrial polyps and uterine fibroids. When contraceptive

methods were investigated, a protective effect of condom use was found. Condom use was more common in women without endometrial polyps (8.1% vs. 3.9%; p=0.044).

The median uterine sizes of both groups were equivalent to 12 weeks pregnancy in the genital examination, ranging from 6-22 weeks in patients with endometrial polyps, and 6-24 weeks in patients without endometrial polyps; p=0.368). As shown in Table 2, no statistical differences were found between the symptoms of women with and without endometrial polyps. Abnormal uterine bleeding rates (56.1% vs. 57.1%; p=0.453), and the mean preoperative hemoglobin levels (11.2±2.4 g/dL vs. 11.4±4.5 g/dL; p=0.874) were similar in both groups.

Table 3 shows the association between the histopathologic findings and the coexistence of endometrial polyps and uterine fibroids. The endometrial polyp rate was higher in women with ≥2 fibroids (OR 1.51; 95% CI: [1.02-2.24]) and with a largest fibroid <8 cm (OR 1.67; 95% CI: [1.10-2.50]). Presence of endometrial hyperplasia (OR 4.00; 95% CI: [1.92-8.33]) and cervical polyps (OR 3.13; 95% CI: [1.69-5.88]) were found significantly associated with the coexistence of endometrial polyps and uterine fibroids. Women with endometrial polyps had higher endometrial hyperplasia rates (9.7% vs. 2.6%; p<0.001) and cervical polyp rates (12.3% vs. 4.2%; p<0.001) than women with uterine fibroids alone. There was no relationship between

Table 1. Demographic, clinical characteristics, and contraception methods of women with endometrial polyps and uterine fibroids, and with uterine fibroids alone

	Endometrial polyp+uterine fibroid (n=155)	Uterine fibroid alone (n=617)	p value
Age ≥45 years	77.9%	68.7%	0.014**
BMI ≥30 kg/m^2	53.8%	49.0%	0.189**
Gravidity	3.8±2.2	3.9±2.2	0.330*
Parity	2.7±1.6	2.7±1.3	0.661*
Previous cesarean section	11.0%	14.1%	0.186**
Diabetes mellitus	10.3%	9.2%	0.389**
Smoking	12.3%	13.5%	0.405**
Hypertension	23.9%	17.5%	0.047**
Postmenopause	9.7%	6.3%	0.761**
IUD use	9.7%	9.9%	0.539**
BTL	3.9%	7.1%	0.094**
Condom use	3.9%	8.1%	0.044**
Hb, g/dL	11.2±2.4	11.4±4.5	0.874*

Data are mean ± SD or %, BMI: Body mass index, IUD: Intrauterine device, BTL: Bilateral tubal ligation, HB: Hemoglobin, SD: Standard deviation, *Student's t-test and **Pearson's Chi-square test were used for statistical analysis

Table 2. Symptoms of women with endometrial polyp and uterine fibroid and with uterine fibroid alone

	Endometrial polyp+uterine fibroid (n=155)		Uterine fibroid alone (n=617)		p value
	n	%	n	%	
Abnormal uterine bleeding	87	56.1	352	57.1	0.453
Pelvic pain	28	18.1	142	23.0	0.110
Pelvic pressure	8	5.2	30	4.9	0.506
Dysmenorrhea	3	1.9	7	1.1	0.204
Urinary tract symptoms	9	5.8	18	2.9	0.361
Bowel symptoms	4	2.6	6	1.0	0.243
No symptoms	16	1.3	62	10.0	0.510

Pearson's Chi-square test were used for statistical analysis

adenomyosis, endometriosis, and endometrial polyps coexisting with uterine fibroids (p>0.05).

Discussion

Endometrial polyps are one of the common causes of abnormal uterine bleeding in premenopausal and postmenopausal women, and its incidence increases with age[10]. The pathogenesis of this pathology is not known exactly. Presence of estrogen and progesterone receptors in polyp specimens suggests that the increased endogenous and exogenous estrogen level plays a role in the endometrial polyp growth[11]. In the literature, association between endometrial polyps and tamoxifen use in breast cancer, postmenopausal hormone therapy, and obesity has been shown[12-14]. Unopposed, high estrogen levels increase the insulin-like growth factor (IGF)-1 level, and the number of IGF-1 receptors within the endometrial tissue and causes endometrial polyp growth[15]. Studies reported that hypertension and hyperglycemia also induce endometrial polyp growth by locally modifying the expression of IGF[2,16]. We investigated the risk factors for the coexistence of endometrial polyps and uterine fibroids and found that the mean age and hypertension rates were significantly higher in women with endometrial polyps coexisting with uterine fibroids. However, there was no relationship between diabetes mellitus, obesity, and coexistence of these two pathologies.

The present study showed the protective effect of condom use against endometrial polyp growth. The rate of condom use was lower in women with endometrial polyps. Cicinelli et al.[17] reported that the presence of endometrial micropolyps was significantly associated with chronic endometritis. Expression of cyclooxygenase-2 and matrix metalloproteinase-2 in immunohistochemical analyses of endometrial polyps has also been shown in some studies[18,19]. These findings suggest that the endometrial polyps may have an inflammatory etiopathogenesis. An inflammatory response to sexually transmitted microorganisms or seminal antigens may play a role in the etiology of endometrial polyps. Korucuoglu et al.[20] reported that human papillomavirus (HPV) infection might cause endometrial polyp growth. Condom use inhibits endometrial polyp growth by preventing the inflammatory response to these antigens.

In the present study, endometrial polyps were more common in women with ≥2 fibroids and largest fibroid size <8 cm. The endometrial cavity should be examined using transvaginal ultrasonography, endometrial biopsy, and saline infusion sonohysterography and/or hysteroscopy in the presence of suspected premalignant and malignant endometrial polyp, before choosing the treatment method. Savelli et al.[21] reported that hyperplastic changes were more common in endometrial polyps. In another study, 248 women with abnormal uterine bleeding were investigated, and hyperplasia was found more common in women with endometrial polyps[22]. Similarly, we found an association between endometrial hyperplasia,cervical polyps, and the coexistence of endometrial polyps and uterine fibroids[21-23].

Indraccolo and Barbieri reported that adenomyosis was associated with endometrial polyps[24]. Their study had limitations

Table 3. Histopathologic findings of women with endometrial polyp and uterine fibroid and with uterine fibroid alone

	Endometrial polyp+uterine fibroid (n=155)		Uterine fibroid alone (n=617)		OR (95% CI)	p value
	n	%	n	%		
Number of fibroids					1.51 (1.02-2.24)	0.023
1	41	26.5	218	35.3		
≥2	114	73.5	399	64.7		
Largest fibroid size					1.67 (1.10-2.50)	0.009
<8 cm	119	76.8	411	66.6		
≥8 cm	36	23.2	206	33.4		
Largest fibroid location						
Submucosal	9	5.8	64	10.4	0.53 (0.26-1.10)	0.051
Intramural	126	81.3	472	76.5	1.34 (0.86-2.08)	0.120
Subserous	20	12.9	81	13.1	0.98 (0.58-1.66)	0.531
Adenomyosis	31	20.0	93	15.1	1.41 (0.90-2.21)	0.087
Endometriosis	12	7.7	30	4.9	1.64 (0.82-3.29)	0.115
Endometrial hyperplasia	15	9.7	16	2.6	4.00 (1.92-8.33)	<0.001
Cervical polyp	19	12.3	26	4.2	3.13 (1.69-5.88)	<0.001

Logistic regression analysis was used for statistical analysis, OR: Odds ratio, CI: Confidence interval

due to the method used to obtain specimens. Adenomyosis was diagnosed in histopathologic examinations of specimens obtained in deep biopsies of the endometrium, reaching the deeper myometrial layer during hysteroscopic resection of endometrial polyps. However, in our study, specimens obtained with hysterectomy were examined and we found no association between endometrial polyps and adenomyosis. Shen et al.[25] noted that the endometrial polyp rate was higher in infertile patients with endometriosis. The authors suggested that patients with endometriosis should be evaluated using hysteroscopy. Our study population included fertile and infertile women, and no association was found between endometriosis and endometrial polyps. Even though approximately 95% of endometrial polyps are benign,resection of endometrial polyps is recommended to rule out malignancy[1,5]. The risk of malignancy and the presence of abnormal uterine bleeding increases in the postmenopausal period[1,26-28]. Histopathologic examinations of endometrial polyps provide the selection of optimal treatment methods in patients with both endometrial polyps and uterine fibroids. Medical management, myomectomy or uterine artery embolization are not appropriate treatment methods in the presence of malignant endometrial polyps.

Uterine fibroids and endometrial polyps are common causes of abnormal uterine bleeding in the reproductive period[29]. Hysterectomy is the definitive therapy for uterine fibroids, whereas hysteroscopic resection is the optimal treatment method for endometrial polyps to reduce the cost and morbidity associated with surgery[1,9]. In the study population, abnormal uterine bleeding rates were similar in women with endometrial polyps and uterine fibroids, and with uterine fibroids alone, and the median uterine size was the equivalent of 12 weeks pregnancy in both groups. Therefore, it was considered that just hysteroscopic polypectomy may not be enough to relieve the abnormal uterine bleeding symptoms and treatment of uterine fibroids in women with both endometrial polyps and fibroids with uteri greater than 12 weeks-pregnancy in size. Nevertheless, further randomized controlled trials are needed to confirm this hypothesis. The present study was not designed to investigate the impact of fibroid size, number, and location in the success of treatment in patients with endometrial polyps and uterine fibroids.

As far as we know, ours is the first study to investigate the coexistence of endometrial polyps and uterine fibroids, and is one of the largest studies on uterine fibroids. However, the major limitation is the retrospective design of the study. Data were obtained retrospectively and control and study groups were nonhomogeneous. Therefore, it is not known whether the defined risk factors were independent risk factors for the coexistence of endometrial polyps and uterine fibroids.

Conclusion

The present study showed that age, number of fibroids, size of the largest fibroid, presence of hypertension, endometrial hyperplasia, and cervical polyps were associated factors with the coexistence of endometrial polyps and uterine fibroids. Condom use has a protective effect against endometrial polyp growth in these patients.

Ethics

Ethics Committee Approval: The study was approved by the Etlik Zübeyde Hanım Women's Health Training and Research Hospital Local Ethics Committee, Informed Consent: Consent form was filled out by all participants.

Peer-review: External and Internal peer-reviwed.

Authorship Contributions

Concept: Tuğba Kınay, Fulya Kayıkçıoğlu, Sevgi Koç, Design: Tuğba Kınay, Fulya Kayıkçıoğlu, Sevgi Koç, Data Collection or Processing: Zehra Öztürk Başarır, Serap Fırtına Tuncer, Funda Akpınar, Analysis or Interpretation: Tuğba Kınay, Literature Search: Tuğba Kınay, Zehra Öztürk Başarır, Writing: Tuğba Kınay, Zehra Öztürk Başarır.

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Utilization of Wilms' tumor 1 antigen in a panel for differential diagnosis of ovarian carcinomas

Over karsinomlarının ayırıcı tanısında Wilms tümör 1'in immünhistokimyasal panelde kullanılması

Dilek Şakirahmet Şen[1], Ayşe Filiz Gökmen Karasu[2], Melin Özgün Geçer[3], Nimet Karadayı[1], Elif Ablan Yamuç[1]

[1]*Lütfi Kırdar Research and Training Hospital, Department of Pathology, İstanbul, Turkey*

[2]*Bezmialem Vakıf University Faculty of Medicine, Department of Obstetrics and Gynecology, İstanbul, Turkey*

[3]*Bezmialem Vakıf University Faculty of Medicine, Department of Pathology, İstanbul, Turkey*

Abstract

Objective: Ovarian metasteses are often mistaken for primary adenocarcinoma. Studies conducted in recent years have focused on a search for an immunohistochemical marker to aid the differential diagnosis primary and metastatic ovarian carcinoma. Our study objective was to study the usefulness of Wilms tumor 1 (WT 1) antigen in this context.

Materials and Methods: The study was conducted at the pathology clinic of Lütfi Kırdar Training and Research Hospital. Deparaffinated blocks of 40 epithelial ovarian tumors, 40 colon adenocarcinomas, and 35 cases of omentum metastases were studied. Cytokeratin 7 (CK 7), cytokeratin 20 (CK 20), and WT 1 were applied to all specimens.

Results: All ovarian adenocarcinomas were stained with CK 7 (100%). Colorectal adenocarcinomas were stained positive with CK 20 in 87.5% of cases. Primary ovarian adenocarcinomas stained positive with WT 1 in 82.5% of the cases and none of the colorectal adenocarcinomas showed staining with WT 1 (0%).

Conclusion: WT 1 can be used in conjuction with CK 7 in the differential diagnosis of ovarian carcinomas.

Keywords: Wilms tumor 1, ovarian cancer, cytokeratin 7, cytokeratin 20

Öz

Amaç: Ovaryen metastazlar primer ovaryen adenokarsinomlar ile karışabilirler. Son yıllarda gerçekleştirilen immünhistokimyasal çalışmalar ayırıcı tanıda fayda sağlayabilecek bir marker bulma konusunda yoğunlaşmıştır.

Gereç ve Yöntemler: Çalışma Lütfi Kırdar Eğitim ve Araştırma Hastanesi'nde gerçekleştirildi. Kırk over adenokarsinomu, 40 kolon adenokarsinomu ve 35 omentum metastazı tanısı almış patoloji preparatı incelenerek Wilms tümör 1 (WT 1), sitokeratin 7 (SK 7) ve sitokeratin 20 (SK 20) ile immünhistokimyasal çalışma yapıldı.

Bulgular: Tüm pimer over adenokarsinomları (%100) SK 7 ile boyanma gösterdi. Kolorektal adenokarsinomların %87,5'i SK 20 ile boyanma gösterdi. Primer over adenokarsinomlarının %82,5'i WT 1 ile boyanma gösterdi. Kolorektal adenokarsinomların hiçbirinde WT 1 ile boyanma izlenmedi.

Sonuç: Adenokarsinomların ayırıcı tanısında WT 1 ile SK 7'nin beraber kullanılması tanıya katkı sağlayabilmektedir.

Anahtar Kelimeler: Wilms tümör 1, over kanseri, sitokeratin 7, sitokeratin 20

Introduction

Ovarian tumors constitute approximately 6% of all malignancies and 30% of all gynecologic malignancies in women[(1)]. Ninety percent of ovarian tumors arise from the surface epithelium of the ovaries. Metastatic ovarian carcinomas make up 3-6% of ovarian malignancies and may originate primarily from genital or nongenital organs[(2)]. Endometrium, fallopian tubes, breasts, as well as gastrointestinal and hematopoietic tissue may be the location of primary tumors. Studies to date have examined patients presenting with ovarian masses; therefore, microscopic metastases have mostly been overlooked. In order to document the incidence of metastatic ovarian tumors, some researchers have comitted to performing autopsies. Fox and Langley[(3)] performed autopsies on 272 women who died of malignancy and discovered that 4.4% of the cases involved ovarian metasteses. One difficulty in diagnosing metastatic ovarian carcinoma is that even after meticulous histologic examination, metasteses are often mistaken for primary adenocarcinoma or vice versa[(4-9)].

Address for Correspondence/Yazışma Adresi: Ayşe Filiz Gökmen Karasu, MD,
Bezmialem Vakıf University Faculty of Medicine, Department of Obstetrics and Gynecology, İstanbul, Turkey
Phone: +90 536 514 41 42 **E-mail:** agokmenkarasu@bezmialem.edu.tr
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Immunohistochemistry with cytokeratin (CK) labelling may be helpful in the differential diagnosis. CKs are intracellular proteins found widely in epithelial tissue. They are classified according to their pH and molecular weight. Expression of these CKs is frequently organ or tissue specific. CKs tend to remain stable when an epithelium undergoes malignant transformation. CK 7 is expressed in ovarian, lung and breast epithelia, but generally not in colon and prostate epithelium. CK 20 is commonly found in colorectal and gastric cancer, transitional cell carcinomas and in Merkel cell carcinomas. Non-mucinous ovarian cancer does not express CK 20. It is often used in combination with CK 7 to distinguish different types of glandular tumors.

Studies conducted in recent years have focused on a search for an immunohistochemical marker to aid the differential diagnoses of primary and metastatic ovarian carcinoma. Our study objective was to study the usefulness of Wilms tumor 1 (WT 1) antigen in this context. WT 1 is a tumor supressor gene (TSG) located on chromosome 11. It has a profound role in genitourinary system development. Unlike other TSGs, WT 1 expression is also found in normal human cells such as mesothelium and fallopian tube epithelium. WT 1 protein can be demonstrated in most ovarian serous carcinomas as well allowing these tumors to be distinguished from other adenocarcinomas. WT 1 also may have a cross reaction with cytoplasmic proteins, so only nuclear staining is considered diagnostic.

Materials and Methods

a. Subject specimens

The study was conducted at the pathology clinic of Lütfi Kırdar Training and Research Hospital. Approval was obtained from the hospital's review board. Deparaffinated blocks of 40 epithelial ovarian tumors and 40 colon adenocarcinomas were studied. In addition, 35 blocks of omental metasteses were included with the aim of determining the primary origin. CK 7, CK 20, and WT 1 were applied to all specimens. Afterwards, archive records of cases with omental metastases were sought and primary disease locations were revealed.

b. Immunohistochemistry

Three-micron-thick sections were cut from the paraffin blocks and placed on poly L-lysine- coated slides and stored in an oven at 37 ºC overnight. The slides were passed through series of alcohol dilutions for 15 minutes each followed by distilled water for rinsing. For antigen retrieval, slides were placed in a plastic coplin jar filled with citrate buffer (pH 6-0) and covered with perforated cling film to minimize evaporation, and then placed in a microwave oven and irradiated at 800 W, 600 W and 360 W, respectively, for five minutes each. Slides were allowed to cool at room temparature for 20 minutes and rinsed. Endogenous peroxidase was blocked (Novacastra protein block RE 7102, Lot 710257). The slides were then rinsed with phospate-buffered saline. The treated slides were immunostained with Wilms Tumor Monoclonal Mouse anti-Human (Leica Band Wilms' Tumor WT 49, 7 mL), CK 7 Monoclonal Mouse anti-Human (NCL-L-CK 7-560 Novacastra 1: 100; Lot: L156019), and CK 20 Monoclonal Mouse anti-Human (NCL-L-CK 20 Novacastra 1: 50; Lot: 6000573). Diaminobenzidine chromogen system was applied on slides for five minutes in order to observe the immune reaction. All slides were rinsed and contrast stained with Meyer's hematoxylin and cleared with xylene. CK 7 and CK 20 expression was cytoplasmic and WT 1 expression was nuclear.

Results

Forty clinically diagnosed cases of ovarian carcinoma, 40 colonic adenoarcinomas, and 35 omental metasteses were examined. The median age of patients with omental metastases was 63.26±11.2 years, with ovarian carcinoma was 53.68±11.68 years, and colonic adenocarcinoma was 59.13±14.30 years.

Primary ovarian adenocarcinomas stained positive with WT 1 in 82.5% of the cases and all colorectal adenocarcinomas were negative with WT 1 (100%) (Table 1). Of the 35 cases of omentum metastases, 54.3% stained positively with WT 1 (Figure 1).

All ovarian adenocarcinomas stained positively with CK 7 (100%) (Figure 2), whereas 92.5% of colorectal adenocarcinomas were negative with CK 7. Of the 35 cases of omentum metastases, 60% stained positively with CK 7.

Primary ovarian adenocarcinomas stained positively with CK 20 in 7.5% (n=3) of cases. These 3 cases were revealed to be mucinous in origin. Colorectal adenocarcinomas stained positively with CK 20 in 87.5% of cases (Figure 3). Out of the 5 specimens of colorectal adenocarcinomas that did not stain, one was of mucinous origin. Of the 35 cases of omentum metastases, 40% stained positively with CK 20.

Archive records revealed that out of the 35 cases of omentum metastases, 22 were ovarian and 13 were of colorectal origin. Nineteen (86.4%) of the 22 ovarian metastases stained positively with WT 1. None of the metastases of colorectal origin stained with WT 1. Twenty-one (95.5%) of the 22 ovarian metastases stained positively with CK 7. None of the metastases of colorectal origin stained with CK 7. Eleven (50%) of the 22 ovarian metastases stained positively with CK 20, along with 10 (76.9%) cases of metasteses of colorectal origin (Table 2).

Five out of the 40 primary ovarian carcinomas were of mucinous origin. These carcinomas showed differences in staining. In three cases, a CK 7+, CK 20+, and WT 1- staining pattern was seen, one was CK 7+, CK 20+, and WT 1+, and the remainder did not stain with any of the markers.

Fifteen out of the 40 primary colorectal carcinomas were of mucinous origin and none of these expressed WT 1 or CK 7 (Table 3). All but one (93.3%) stained positively with CK 20.

Disussion

Various studies have shown that metastatic ovarian carcinomas generally stain positively with CK 7 and negatively with CK 20, whereas the opposite is true for colorectal carcinomas. However, mucinous carcinomas frequently express both antigens and can present a diagnostic challenge[10,11]. Groisman et al.[12] researched CdX2 in order to aid the differential diagnosis of primary and secondary colorectal adenocarcinomas. The authors suggested that CdX2 was more specific than CK 20 for colorectal adenocarcinoma and that inclusion of CdX2 in antibody panels to distinguish between primary and secondary epithelial colorectal malignancies may be helpful.

In our study, 87.5% of primary colorectal adenocarcinomas and 76.9% of colorectal omental metastases stained positively with CK 20. These percentages are lower than Groisman's results but we believe that mucinous carcinomas accounted for the discrepancy[12]. Ovarian carcinomas did not stain with

Table 1. Immunohistochemistry staining of the specimens

	Omentum		Ovary		Coloerctal			
	n	%	n	%	n	%	χ^2	p
WT 1								
Negative	16	45.7	7	17.5	40	100		
Positive	19	54.3	33	82.5			56.62	<0.001
CK 7								
Negative	14	40.0			37	92.5		
Positive	21	60.0	40	100	3	7.5	69.72	<0.001
CK 20								
Negative	21	60.0	37	92.5	5	12.5		
Positive	14	40.0	3	7.5	35	87.5	52.22	<0.001

WT: Wilms tumor, CK: Cytokeratin

Table 2. Immunohistochemistry staining of omental metastases and their primary origins

Primary origin	Colorectal		Ovarian			
	n	%	n	%	χ^2	p
WT 1						
Negative	13	100.0	3	13.6		
Positive	0	0	19	86.4	24.56	<0.001
CK 7						
Negative	13	100.0	1	4.5		
Positive	0	0	21	95.5	31.02	<0.001
CK 20						
Negative	3	23.1	11	50.0		
Positive	10	76.9	11	50.0	14.01	<0.001

WT: Wilms tumor, CK: Cytokeratin

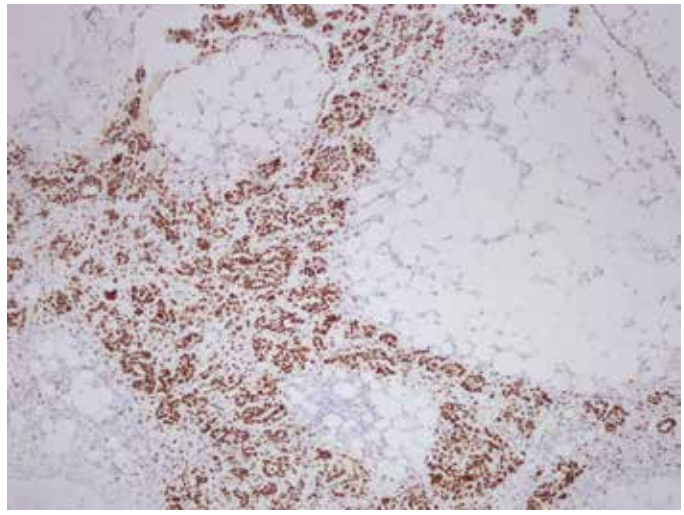

Figure 1. Omental metastasis of primary ovarian carcinoma stained with WT 1

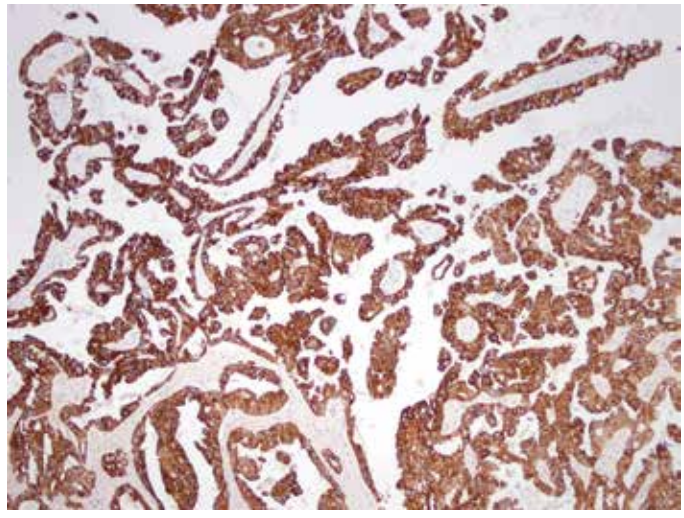

Figure 2. Serous ovarian carcinoma stained with cytokeratin CK 7

Table 3. Staining patterns of colorectal adenocarcinomas

	Non mucinous		Mucinous			
	n	%	n	%	χ^2	p
WT 1						
Negative	25	100.0	15	100		
Positive	0	0	0	0		
CK 7						
Negative	22	88.0	15	100.0		
Positive	3	12.0	0	0		0.279
CK 20						
Negative	4	16.0	1	6.7		
Positive	21	84.0	14	93.3		0.633

WT: Wilms tumor, CK: Cytokeratin

CK 20 in 92.5% of the cases. Whilst ovarian nonmucinous adenocarcinomas do not express CK 20, CK 20 expression of mucinous ovarian carcinomas has been studied. Loy et al.[13] reported 60% positive staining results with CK 20 in serous ovarian carcinomas. In contrast, Berezowski et al.[10] showed that differentiated colorectal adenocarcinomas did not show a positive CK 20 staining pattern. In the above mentioned study, Groisman was searching for a more specific marker than CK 20 for colorectal carcinoma. In our study, we had a similar aim to introduce WT 1 in an antibody panel for ovarian carcinoma. All of the ovarian adenocarcinoma slides stained positively with CK 7 and 82.5% stained with WT 1. However, CK 7 expresion can also be seen with gastrointestinal, lung, and breast adenocarcinomas. These results have led us to the possibility of using these markers in adjunction.

Ordenez[14] applied WT 1 staining to 135 adenocarcinomas including ovarian, colorectal, renal, thyroid, and prostate origin. Among the adenocarcinomas, only ovarian adenocarcinomas expressed WT 1. Loeb et al.[15] used western blotting as well as immunohistochemistry and showed WT 1 positivity in 27 out of 31 breast adenocarcinomas. As a result of their study, WT 1 was questioned as an oncogene for breast cancer rather than a tumor supressor gene. Miyoshi et al.[16] proposed that high expression of WT 1 was a poor prognostic factor for breast adenocarcinoma. Other researchers have suggested that altered expression of WT 1 has a role in breast cancer development[17]. Yet, other researches concluded with contradictory results. Harry Hwang et al.[18] applied WT 1 to 118 breast cancer tissue specimens and yielded postive results in only 8 cases. Inoue et al.[19] showed that WT 1 was a prognostic marker for leukemia. Hylander et al.[20] demonstrated that WT 1 played a prognostic role in ovarian adenocarcinoma and that its expression was correlated with tumor grade and stage but not with survival. Another study of WT 1 on ovarian tissue by Shimizu et al.[21] found positive WT 1 staining with ovarian surface epithelium, inclusion cysts, and fallopian tubes, but not with cervical or endometrial epithelial tissue.

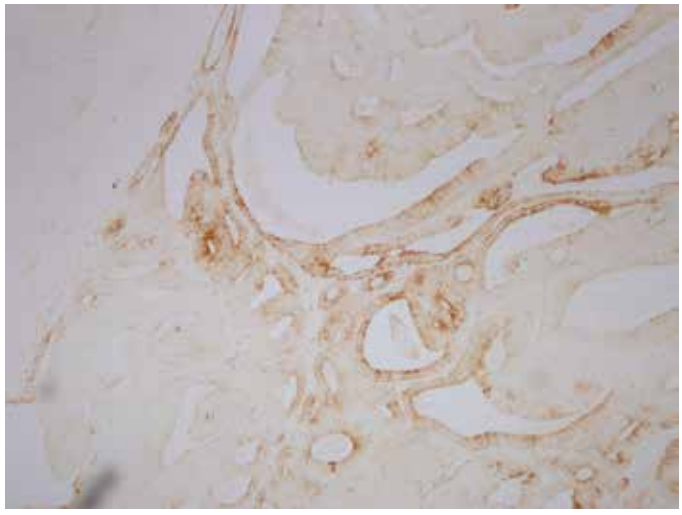

Figure 3. Colon adenocarcinoma stained with cytokeratin 20

In our study we have shown that CK 7 was a more sensitive marker than WT 1 for ovarian carcinoma; however, CK 7 expression is frequently seen in the gastrointestinal system, lung, and breast tumors. We can hypothesise that WT 1 can be used beacuse our study showed that 82.5% ovarian tumors and none of the colerectal carcinomas expressed WT 1.

To summarize, CK 20 does not differentiate mucinous or nonmucinous colorectal carcinoma. Regarding mucinous tumors, our markers CK 7, CK 20, and WT 1 were not useful. WT 1 can be used in conjuction with CK 7 in the differential dianosis of ovarian carcinomas.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Kartal Training and Research Hospital, Informed Consent: All the participants filled out consent forms.
Peer-review: Internal and Externally peer reviewed.

Authorschip Contributions

Surgical and Medical Practices: Deparaffinated blocks of pathology specimens were used, Concept: Dilek Şakirahmet Şen, Ayşe Filiz Gökmen Karasu, Melin Özgün Geçer, Nimet Karadayı, Elif Ablan Yamuç, Design: Dilek Şakirahmet Şen, Ayşe Filiz Gökmen Karasu, Nimet Karadayı, Elif Ablan Yamuç, Data Collection or Processing: Dilek Şakirahmet Şen, Nimet Karadayı, Elif Ablan Yamuç, Analysis or Interpretation: Dilek Şakirahmet Şen, Ayşe Filiz Gökmen Karasu, Literature Search: Dilek Şakirahmet Şen, Ayşe Filiz Gökmen Karasu, Melin Özgün Geçer, Nimet Karadayı, Elif Ablan Yamuç, Writing: Dilek Şakirahmet Şen, Ayşe Filiz Gökmen Karasu.
Conflict of Interest: No conflict of interest was declared by the authors.
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Case Report / Olgu Sunumu

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A novel approach for congenital absence of the uterine cervix: Office hysteroscopic versapoint canalization using real-time trans-abdominal sonography guidance

Uterin serviksin konjenital yokluğuna yeni bir yaklaşım: Transabdominal ultrasonografi rehberliği ile ofis histereskopisinde versapoint ile servikal kanalizasyon

Bülent Haydardedeoğlu, Pınar Çağlar Aytaç

Başkent University Faculty of Medicine, Department of Obstetrics and Gynecology, Division of Reproductive and Endocrinology Unit, Adana, Turkey

Abstract

Herein, we report a novel technique for cervical agenesis via office hysteroscopy using Versapoint using real-time trans-abdominal sonography guidance. Fourteen days after the canalization procedure, a second hysteroscopy was performed to remove the silicone catheter and insert a Cupper T380a intrauterine device, which aimed to prevent a neocervical canal occlusion. This is the first case report of a patient with congenital cervical agenesis undergoing canalization with Versapoint in an office hysteroscopy; laparoscopy was not performed for assistance.

Keywords: Cervical agenesis, hysteroscopy, Versapoint

Öz

Bu olgu sunumunda gerçek zamanlı trans-abdominal sonografi rehberliğinde Versapoint kullanılarak ofis histeroskopi yoluyla servikal agenezi için yeni bir teknik sunmayı amaçladık. Kanalizasyon işleminden on dört gün sonra, silikon kateteri kaldırmak ve bir neoservikal kanal tıkanıklığını önlemek amacıyla uterin kaviteye Bakır T380a rahim içi araç yerleştirmek için ikinci bir histereskopi uygulandı. Bu olgu konjenital servikal agenezi olan bir hastada ilk defa laparoskopi yardımı olmadan versa-point ile ofis histereskopisinde kanalizasyon uygulamasının olgu raporudur.

Anahtar Kelimeler: Servikal agenezi, histereskopi, Versapoint

Introduction

Congenital absence of uterine cervical agenesis is an extremely rare anomaly among all urogenital tract malformations and occurs in 1 in 80.000-100.000 births[1]. The first presenting symptom of cervical agenesis is primary amenorrhea with secondary sex characterstics, occasional cyclic lower abdominal pain, and commonly-occurring retrograde menstruation. A total abdominal hysterectomy remains the primary choice of treatment in these patients for relieving symptoms of retrograde menstruation and preventing concomitant endometriosis. However, reconstructive surgery for saving the uterus is performed by only a few expert surgeons worldwide. This skillful surgery has been reported in the current literature as a case series[2-6]. Recently, Kriplani et al.[7] reported a new case series of laparoscopic-assisted uterovaginal anastomosis in 14 patients. Laparoscopy is usually performed to assist in reconstruction of the utero-vaginal pathway[8].

Herein, we report a novel technique for cervical agenesis in an office hysteroscopy using Versapoint with real-time trans-abdominal sonography guidance. After reconstructing the cervical canal, a silicone catheter remained for 14 days and was replaced by a Cupper-T 380 a intrauterine device (IUD) to prevent neocervical canal obliteration following a second hysteroscopic re-evaluation. At the 9-month follow-up, the patient was relieved of severe abdominal pain and has regular menstruation. This is the first case report of a patient with congenital cervical agenesis in whom laparoscopy was not performed for assistance.

Address for Correspondence/Yazışma Adresi: Pınar Çağlar Aytaç, MD,
Başkent University Faculty of Medicine, Department of Obstetrics and Gynecology, Division of Reproductive and Endocrinology Unit, Adana, Turkey
Phone: +90 322 344 44 44/1444-5 **E-mail:** pinarcag1976@yahoo.com
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Case Report

A woman aged 21 years was referred to Adana Başkent University Faculty of Medicine, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology/IVF Unit and Endoscopic Surgery with primary amenorrhea and long-standing severe cyclic pelvic pain. The patient had been married for 3 years but was divorced due to infertility. She went laparotomy for reconstruction 3 years ago, but this was unsuccessful. She was referred to a university hospital 2 years ago for reconstruction of an utero-vaginal anastomosis and underwent a laparoscopy for canalization, which also failed. On examination, she had a blind-ending vagina and normal secondary sexual characteristics. A karyotype analysis and other hormonal parameters had been evaluated as normal (normal female, 46 XX) at a previous university hospital. She was accepted for the operation and was admitted for surgery to canalize the uterovaginal junction. Institutional review board approval was not obtained because the approval of the patient was obtained.

Surgical Technique

After induction of general anesthesia and administration of an appropriate prophylactic antibiotic, the patient was prepared for surgery and placed in the supine position in the operating room. Her legs were placed in a lithotomy position at a 30° angle at the hips. The vulva, perineum, legs, and vagina were cleaned and draped. After inserting a speculum, suprapubic pressure was exerted to force the uterine body down. After palpation of the utero-vaginal junction, a transverse incision was made through the so-called vesico-cervical fascia, and the muscular layer of the bladder was removed upwards (Figure 1). The dense thick body of the lower uterine segment was visualized, and a 3 cm longitudinal incision (1 cm in depth) was made through the lower part of the uterine body (Figure 2). Thereafter, the bladder was filled using an office hysteroscope to visualize the trans-abdominal sonography.

A 4 mm office hysteroscope (Karl Storz) was inserted into the previous linear incision with the assistance of gynecologic sonographer, and Versapoint cautery was performed to cut the blind end of the uterine body. The office hysteroscope was pushed forward with the cutting mode of the twizzle type Versapoint (Gynecare, Ethicon) with 0.9% NaCl distention medium through the ultrasonographically visible triple line (Figure 3). Hegar buji dilatators were used a few times to dilate the canal appropriately. After several attempts to reach the uterine fundus, the uterine cavity was visualized with the

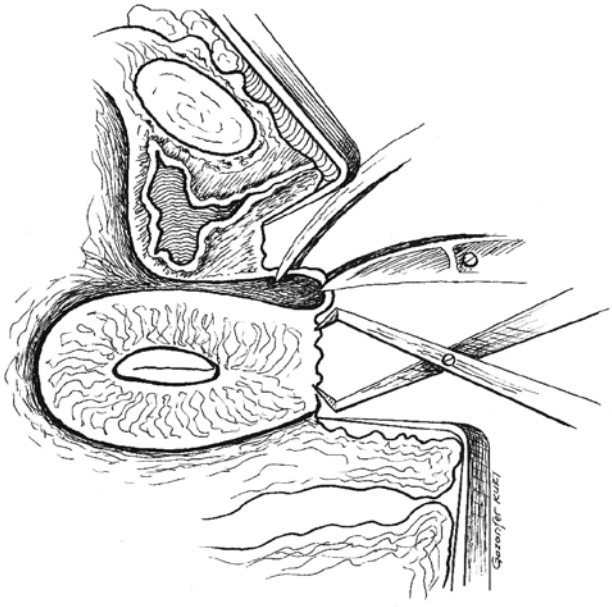

Figure 1. Dissection plane to create neocervix

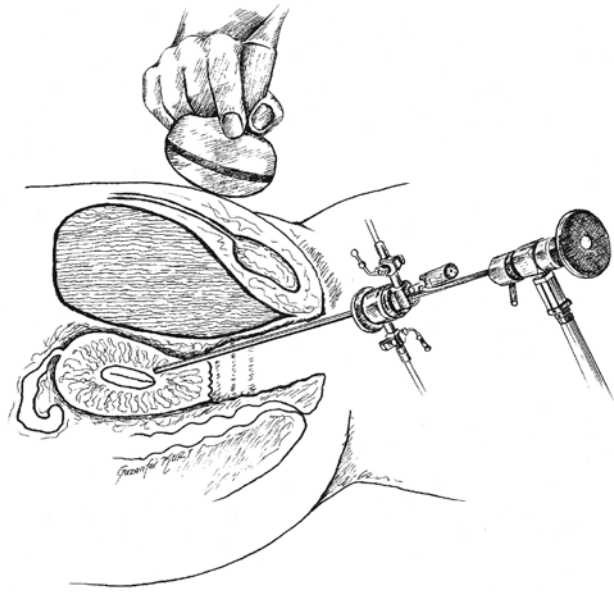

Figure 2. Hysterescopic instrumentation during uterine cavitiy access

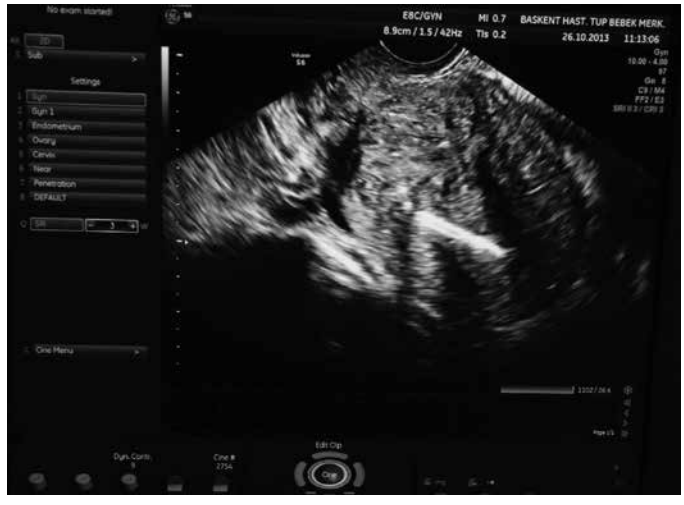

Figure 3. Ultrasonographic image of intrauterine device in the uterine cavity and the neocervix extending in the lower part of uterus

hysteroscope. Hegar buji dilatators were used to dilate the newly-formed canal. A silicone catheter was inserted into the uterine cavity and filled with 10 mL of saline to prevent obliteration of the canal. The vaginal mucosa was closed separately using 2/0 Vicryl.

Fourteen days after the canalization procedure, a second hysteroscopy was performed to remove the silicone catheter and insert a Cupper T380a IUD, which aimed to prevent a neocervical canal occlusion. An oral contraceptive (Yasmin, İstanbul, Turkey) was prescribed to the patient to schedule the first menstruation. The patient menstruated regularly for 4 days 25 days later. She was re-examined 10 days after ending the first menstruation; only a pinpoint neocervical orifice and the string of the IUD was visible (Figure 1, 2). The patient has had regular menstrual cycles at 27-day intervals and 4 days of bleeding since the first menstruation, without the long-standing pelvic pain or infection.

Discussion

Operative management of congenital uterine cervical agenesis is a challenging issue. With the advancement of endoscopic surgery skills, laparoscopic assistance has gained importance during the uterovaginal canalization procedure for cervical agenesis[7,8]. This extremely rare uterine anomaly has been corrected by several operative techniques in which earlier case series reported high recurrence and high complication and infection rates, particularly concomitant with vaginal agenesis[9,10]. Nguyen et al.[6] used a vaginal mucosa-lined polytetrafluoroethylene graft to prevent closure of the reconstructed cervical canal; we used an IUD string and this was also effective.

This is the first case report of a Versapoint hysteroscopy without operating on the abdomen in terms of laparoscopy or laparotomy. Instead, real-time trans-abdominal ultrasound guidance was used to reach the correct route to the uterine cavity. Ultrasound guidance is less costly than laparoscopic guidance and adds no additional cost over hysteroscopy alone. In our clinic, ultrasonic guidance is routinely used throughout hysteroscopic synechiolysis for severe intrauterine adhesions. Some authors have also reported that ultrasound is the optimal choice for guidance during a difficult hysteroscopy[11,12].

The Versapoint, which uses a 4 mm office hysteroscope, is a safe and effective alternative to the resectoscope. It is used predominantly in nulligravida women, particularly in those with cervical canal stenosis. The superiority of the office hysteroscope over the resectoscope in terms of smaller diameter made it the first choice in the present case. Only Versapoint could be used in such a narrow area. Furthermore, the superiority of Versapoint over resectoscopes during operative hysteroscopy has been shown by Litta et al.[13].

Future fertility with this type of new technique is a challenging point. We do not know what will happen to the cervical canal after removal of the IUD. Cervical canal obliteration will be the main threatening complication after IUD removal. The obliteration of the newly-formed cervix can be corrected by repetitive hysteroscopy and a vaginal mucosa-lined polytetrafluoroethylene graft can be used if we face cervical canal obliteration[6]. In case of infertility, intrauterine insemination seems to be successful after this type of operation. However, transabdominal cerclage would be reasonable for preventing preterm labor in such patients.

The concomitancy of hematometra, hematosalpinx, endometriosis, and its complications would be seriously relieved after this type of operation. Our patient insisted on reporting dramatic relief of cyclic pain, which was due to correction of outflow obstruction. However, the addition of laparoscopic operation to congenital cervical agenesis can be superior for the evaluation of endometriosis staging. The advancement of endometriosis in such young patients is also controversial.

This novel approach is a safe, cheap, and feasible technique for congenital uterine cervical agenesis. The simplicity of this operation is in the presence of the blind-ending vagina. This technique is not suitable in cases of concomitant cervical and vaginal agenesis, in which laparoscopy should be used. The obstetric outcomes of such reconstructive surgery remain to be determined. Thus, further studies should evaluate the long-term gynecologic and obstetric outcomes following such an operation.

Ethics

Informed Consent: Informed consent was filled out by our patient.
Peer-review: Internal peer-reviwed.

Authorship Contributions

Surgical and Medical Practices: Bülent Haydardedeoğlu, Pınar Çağlar Aytaç, Concept: Bülent Haydardedeoğlu, Pınar Çağlar Aytaç, Design: Bülent Haydardedeoğlu, Pınar Çağlar Aytaç, Data Collection or Processing: Bülent Haydardedeoğlu, Pınar Çağlar Aytaç, Analysis or Interpretation: Bülent Haydardedeoğlu, Pınar Çağlar Aytaç, Literature Search: Bülent Haydardedeoğlu, Pınar Çağlar Aytaç, Writing: Bülent Haydardedeoğlu, Pınar Çağlar Aytaç.
Conflict of Interest: No conflict of interest was declared by the authors.
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Case Report / Olgu Sunumu

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Turk J Obstet Gynecol 2016;13:46-9

Vesicocutaneus fistula after cesarean section-a curious complication: Case report and review

Sezeryan sonrası ilginç nadir bir komplikasyon vezikokutanöz fistül: Olgu sunumu ve derleme

Burak Tatar[1], Ebru Erdemoğlu[2], Sedat Soyupek[3], Yakup Yalçın[1], Evrim Erdemoğlu[1]

[1]*Süleyman Demirel University Faculty of Medicine, Department of Gynecologic and Oncology, Isparta, Turkey*

[2]*Isparta Maternity Hospital, Clinic of Obstetrics and Gynecology, Isparta, Turkey*

[3]*Süleyman Demirel University Faculty of Medicine, Department of Urology, Isparta, Turkey*

Abstract

Vesicocutaneous fistulas are very rare pathologies in the urinary tract. We present the second case of a vesicocutaneus fistula after cesarean section, and discuss strategies for prevention, diagnosis, and treatment of this exceptional complication. A woman with a vesicocutaneous fistula after cesarean delivery was admitted and diagnostic tests including fluoroscopy, magnetic resonance imaging (MRI), and reconstructed MRI revealed the fistula tract and an urachal anomaly. The patient was treated through excision of the fistula tract. Laparotomy should be performed carefully, and the surgeon should be aware of the urachus. Inadvertent trauma to the urachus during laparotomy might cause serious unexpected complications. Possible etiologic factors for vesicocutaneous fistulae, prevention, and treatment methods are discussed.

Keywords: Cesarean delivery, vesicocutaneous fistula, urachus, diagnosis, treatment

Öz

Vezikokutanöz fistüller, idrar yollarında çok nadir olarak görülen patolojilerdir. Sezaryen sonrasında meydana gelen bir vezikokutanöz fistülün olgu sunumunu ilk defa paylaşmaktayız. Ayrıca bu sıradışı komplikasyonun önlenmesi, tanısı ve tedavisi için stratejiler tartışılmıştır. Sezaryen sonrası vezikokutanöz fistül ile kabul edilen hastaya tanı için floroskopi, manyetik rezonans (MR), rekonstrükte MR yapılmıştır ve urakal anomali saptanmıştır. Hasta, fistül yolunun eksizyonu ile tedavi edilmiştir. Laparotomi dikkatle yapılmalıdır ve cerrah urakusun farkında olmalıdır. Laparotomi sırasında urakusun yanlışlıkla travmatize olması, ciddi ve beklenmeyen komplikasyonlara neden olabilir. Vezikokütanöz fistülün etiyolojisinde rol oynayabilen faktörler, bu durumun önlenmesi ve tedavi yöntemleri tartışılmıştır.

Anahtar Kelimeler: Sezaryen doğum, vezikokutanöz fistül, urakus, tanı, tedavi

PRECIS: We present the second reported case of vesicocutaneus fistula occurring after cesarean section, and discuss strategies for prevention, diagnosis, and treatment of this exceptional complication.

Introduction

The cesarean delivery rate has risen from 4.5 percent to 31.8 percent of all deliveries[1]. Lower urinary tract injuries are not infrequent and may occur during this procedure. If not intraoperatively detected and repaired, diagnosis will be delayed and a genitourinary fistula may be encountered later. There are case reports of vesico-vaginal, uretero-vaginal, vesico-uterine fistulas after cesarean section. There are also reported cases of uretero-vesico-cervical and vesico-peritoneal fistulas[2-4]. Vesicocutaneous fistulas are very rare pathologies in the urinary tract. Trauma, neoplasia, inflammation, and iatrogenic injury are the most frequent causes. Anomalies of the urachus may predispose patients to injury and subsequent fistula formation during surgery due to the distorted anatomy. We present the second case of vesicocutaneus fistula, which occurred after cesarean section, and discuss strategies for prevention, diagnosis, and treatment of this exceptional complication.

Case Report

A gravida 2, para 2 woman aged 44 years with a history of two cesarean sections was referred because of recurrent urinary

Address for Correspondence/Yazışma Adresi: Evrim Erdemoglu, MD,
Düleyman Demirel University Faculty of Medicine, Department of Gynecologic and Oncology, Isparta, Turkey
Phone: +90 246 211 21 44 **E-mail:** evrimmd@yahoo.com

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tract infection and urinary leakage through the abdomen. In her past medical history, she had Sjogren's syndrome and optic neuritis. In her past surgical history, she had a bladder injury in a caesarean section, which was repaired with a primary suture. One month later, she presented with a 10 cm subcutaneous hematoma at its largest dimension. The hematoma was drained surgically, and during the exploration, no source of bleeding was found. Four months later (in total, five months after the cesarean section), she was admitted to the hospital and referred for urinary leakage through the abdomen, about 5 cm below the level of umbilicus. The leakage was periodic and she had an episode of subcutaneous abscess, which was managed conservatively using antibiotics and non-steroidal anti-inflammatory drugs.

A fistula tract was observed in a retrograde fluoroscopic examination; however, the distal end of the fistulous tract was not clear (Figure 1). An ultrasound examination was also not helpful to clarify the lesion. Contrast-enhanced magnetic resonance (MR) urography (Figure 2) revealed a defect of 1.2 cm on the anterior wall of the bladder in the midline. Between this defect and subcutaneous fatty tissue, a fistula tract of 2 cm at its widest diameter was evident. In the subcutaneous fatty tissue, a 6x6.4x3.7 cm collection was directly related with the fistula tract. There was inflammation and possible infection surrounding the collection due to the dense contrast enhancement.

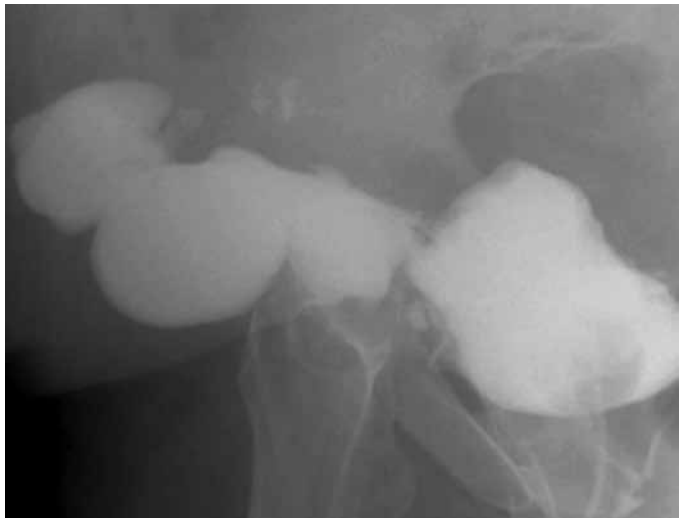

Figure 1. Fluoroscopic lateral view

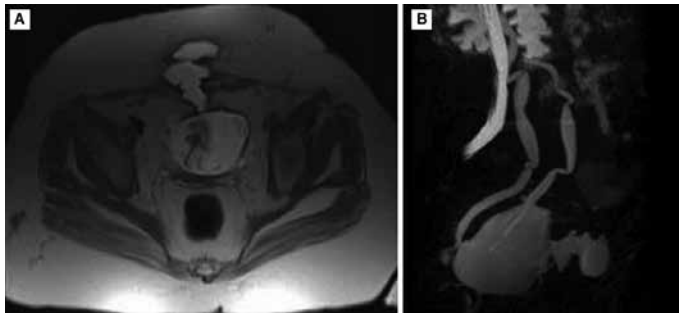

Figure 2. A: T2 Weighted image of the vesico-cutaneous fistula. B: Reconstructed lateral-oblique magnetic resonance image. Fistula tract is clearly seen

The patient underwent a laparotomy with the plan for excision of the fistula tract and repairing the bladder defect. A suprapubic incision parallel to the Langer's lines of the skin was made with a 1.5-2 cm margin with the fistulous tract. The fistula tract was about 12 cm in length and 4 cm wide, and was totally excised with the involved skin (Figure 3, 4). The defect on the dome of the bladder, which is apart from the trigon, was closed in 3 layers. The rectus fascia was closed with 1-0 Vicryl Subcuticular tissue was repaired with interrupted 2-0 Vicryl and the skin was repaired with 3-0 Prolene sutures. Her two-month follow-up after the surgery was unremarkable.

Discussion

Vesicocutaneus fistulas are rare. Their exact incidence is not known due to their rarity. Trauma, neoplasia, inflammation, and

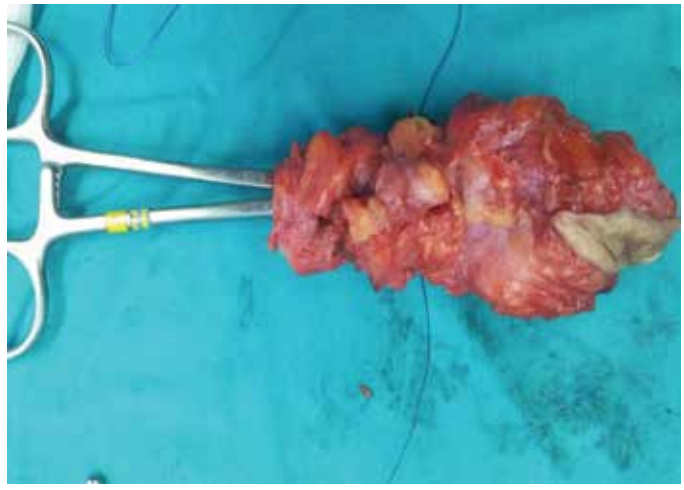

Figure 3. Fistula tract totally excised with the outer edge on the skin

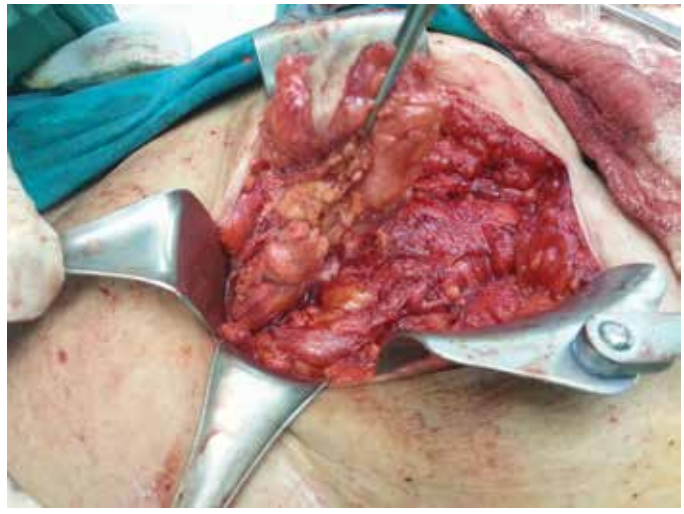

Figure 4. Excision of the fistula tract via laparotomy

iatrogenic injury are the most frequent causes of these urinary fistulas[1,5]. Due to the rarity of vesicocutaneus fistulas, their risk factors are not clearly identified. Pelvic radiation, radical hysterectomies, pelvic fractures, hip arthroplasties, bladder calculus, and inguinoscrotal hernia operations are reported risk factors[6]. Actinomyces infections and factitious disorders have also been reported to cause vesicocutaneous fistula[7,8]. Unrecognized urachal anomalies may be a predisposing risk factor during surgical procedures. Cesarean delivery might be a risk factor due to the nature of the procedure, compared with vaginal delivery. There was an urachal anomaly, a possible urachal diverticula that was asymptomatic until the surgical intervention in our case. Urachal anomalies are very rare. Their true incidence is unknown, but is estimated to be between 0.015 to 0.13 in 1000 births according to a large case series[6,7]. They may be asymptomatic, especially when presenting as a urachal cyst or diverticulum. These anomalies may predispose a patient to injury during abdominal surgery, especially in cesarean section. Inadvertent injury to the urachus with a diverticulum may be complicated by vesicocutaneous fistula.

Radiographic imaging is the traditional method to identify a fistula. Fluoroscopy may identify the lesion, but it may not clarify it. Sonography was one of the imaging modalities used in the past, but due to its poor sensitivity, especially in identifying complexity, size, and multiplicity, it is rarely used now for identification of fistulae[8]. Magnetic resonance imaging and computed tomography (CT) are currently the imaging modalities of choice for the initial evaluation of patients with suspected pelvic fistulae[9]. MR seems to be one of the most sensitive methods to define the exact location and complexity of a fistula tract, with more than 90% sensitivity and correlates well with surgical findings[10]. Multi-detector CT is the choice for patients who are unable to tolerate fluoroscopy or MR imaging. As in our case, the best imaging modality was contrast-enhanced magnetic resonance (MR) imaging, which clearly identified the exact location of the lesion and its relation with the surrounding tissues.

There is one case report of vesicocutaneus fistula secondary to cesarean hysterectomy from Pakistan by Toufique and Merani[11]. It was treated with conservative management and an indwelling bladder catheter was left for 3 weeks and parenteral antibiotics were given. The authors reported that the fistula tract closed spontaneously. A conservative approach may be tried in small fresh fistulas. We chose a curative surgical approach for a major fistula. The treatment approach depends on type of the fistula, symptoms, the time passed from injury, and the patient. For vesico-vaginal fistula, fistulectomy is the preferred management method. Delayed repair is the classic approach, but some articles advocated immediate repair because of better results[12-14]. Conservative management is also described, but an option not chosen frequently[15]. When the case is a uretero-vaginal fistula, conservative management can be considered initially, especially if the patient is appropriate for ureteral stenting, otherwise surgery is the definitive treatment method[16]. Vesicocutaneous fistulas are very rare, and to the best of our knowledge, there has been no report of a vesicocutaneus fistula occurring secondary to cesarean section and as a consequence, the optimal management strategy is unknown.

Although conservative management can be reasonable in asymptomatic patients with urachal remnants, fistulectomy with primary closure of the bladder is a logical approach, especially for symptomatic patients with recurrent infections as in our case[17]. Laparotomy should be performed carefully, and the surgeon should be aware of patent urachus. Inadvertent trauma to the urachus during laparotomy might be a cause for serious unexpected complications.

Ethics

Informed Consent: A Consent form was filled out by all participants.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Sedat Soyupek, Evrim Erdemoğlu, Concept: Evrim Erdemoğlu, Sedat Soyupek, Design: Evrim Erdemoğlu, Burak Tatar, Ebru Erdemoğlu, Data Collection or Processing: Burak Tatar, Analysis or Interpretation: Burak Tatar, Ebru Erdemoğlu, Literature Search: Burak Tatar, Yakup Yalçın, Writing: Burak Tatar, Evrim Erdemoğlu, Ebru Erdemoğlu.
Conflict of Interest: No conflict of interest was declared by the authors.
Financial Disclosure: The authors declared that this study has received no financial support.

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Case Report / Olgu Sunumu

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Prenatal diagnosis of sirenomelia in the first trimester: A case report

Birinci trimesterda sirenomelili olgunun prenatal tanısı: Olgu sunumu

Yasin Ceylan, Yasemin Doğan, Sebiha Özkan Özdemir, Gülseren Yücesoy

Kocaeli University Faculty of Medicine, Department of Obstetrics and Gynecology, Kocaeli, Turkey

Abstract

Sirenomelia or "mermaid syndrome" is a rare congenital syndrome characterized by the anomalous development of the caudal region of the body. We present a case of sirenomelia diagnosed in the first trimester using two-dimensional and three-dimensional ultrasonographic examination. A nulliparous woman aged thirty years was referred to our perinatology unit for evaluation because of oligohydramnios at 12 weeks of gestation. Her medical history was unremarkable. There was no family history of genetic abnormalities. We identified a single lower extremity and severe oligohydramnios, which are characteristics of sirenomelia. Sirenomelia, a developmental defect involving the caudal region of the body, is associated with several internal visceral anomalies. Sirenomelia is fatal in most cases due to the characteristic pulmonary hypoplasia and renal agenesia. Prenatal diagnosis of sirenomelia may be difficult in the second or third trimester because of the severe oligohydramnios; it should be easier to diagnose sirenomelia in the first trimester.
Keywords: Sirenomelia, congenital syndrome, prenatal diagnosis

Öz

Sirenomeli veya "denizkızı sendromu" vücudun kaudal bölgede anormal gelişimi ile karakterize nadir görülen bir konjenital bir sendromdur. İlk trimesterde iki boyutlu ve üç boyutlu ultrasonografi muayenesi ile tanı konulmuş sirenomeli bir olgu sunduk. Otuz yaşındaki nullipar kadın 12. gebelik haftasında oligohidramnios nedeniyle bizim perinatoloji ünitesine sevk edildi. Hastanın öyküsünde herhangi bir özellik yoktu. Ailesinde herhangi bir genetik anomali öyküsü yoktu. Bir tek alt ekstremite ve şiddetli oligohidramnios ile karakterize sirenomeli tanısını tanımladık. Sirenomeli, çeşitli iç organ anomalileri ile birliktelik gösteren vücudun kaudal bölgesini kapsayan gelişimsel bozukluktur. Sirenomeli pulmoner hipoplazi ve renal agenezi nedeniyle ölümcül bir anomalidir. Ciddi oligohidroamniosa bağlı olarak ikinci ve üçüncü trimesterda prenatal tanısı zor olabilir. ilk trimesterda tanı konulması daha kolaydır.
Anahtar Kelimeler: Sirenomeli, konjenital sendrom, prenatal tanı

PRECIS: A diagnosis of sirenomelia may be easier to make during the first trimester because the amniotic fluid volume is relatively normal. During later periods, ultrasonographic diagnosis may be prevented because of severe oligohydramnios due to renal agenesis or dysgenesis..

Introduction

Sirenomelia or "mermaid syndrome" is a rare congenital syndrome characterized by the anomalous development of the caudal region of the body[1]. The syndrome has been reported to occur 1 in 60 000 live births, and predominantly in male fetuses[2]. Progressive oligohydramnios is usually the first sign of this syndrome in the second trimester because of renal abnormalities[3]. Sirenomelia should be easier to diagnose in the first trimester. We present a case of sirenomelia diagnosed in the first trimester using two-dimensional and three-dimensional ultrasonographic examination.

Case Report

A nulliparous woman aged 30 years was referred to our perinatology unit for evaluation because of oligohydramnios at 12 weeks of gestation. An antenatal ultrasonographic scan revealed a single live fetus with oligohydramnios. The upper half of the fetus appeared normal with both upper extremities seen separately and moving normally. However, the lower extremities appeared to be fused together in fixed extension and mobility at the hip and knee joints was restricted (Figure 1). A single umbilical artery was demonstrated using color

Address for Correspondence/Yazışma Adresi: Yasin Ceylan, MD,
Kocaeli University Faculty of Medicine, Department of Obstetrics and Gynecology, Kocaeli, Turkey
Phone: +90 535 748 97 29 **E-mail:** md.yasinceylan@yahoo.com
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Doppler (Figure 2). Thus, the diagnosis of sirenomelia was made prenatally. Medical termination of pregnancy was performed with the informed decision of the parents. On postnatal examination, the fetus weighed 150 grams. External examination revealed fusion of both lower extremities (Figure 3). Based on the external examination, sirenomelia was diagnosed.

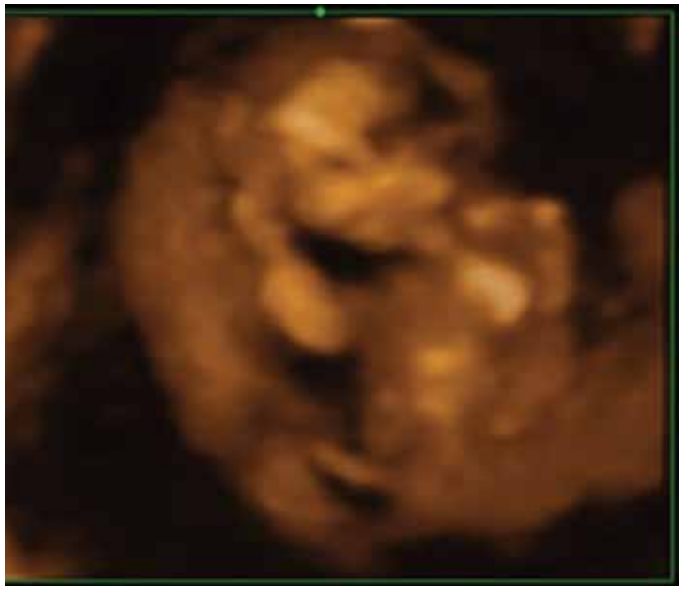

Figure 1. Three dimensional ultrasonographic image shows normal upper limbs and single lower limb

Figure 2. Color doppler ultrasonographic image shows single umblical artery

Discussion

Sirenomelia, a developmental defect that involves the caudal region of the body, is associated with several internal visceral anomalies. It is associated with renal agenesis, sacral agenesis, anorectal atresia, imperforate anus, absent urinary bladder, lumbosacral and pelvic bone abnormalities, single umbilical artery, and ambiguous genitalia. Sirenomelia is fatal in most cases because of the characteristic pulmonary hypoplasia due to the severe oligohydramnios[4]. Two theories have been proposed to explain the etiopathogenesis of sirenomelia; the vascular steal hypothesis and the defective blastogenesis hypothesis. Normally, the umbilical cord contains two arteries that originate from the iliac arteries, which return blood to the placenta. In cases of sirenomelia, the umbilical artery is single and arises from the abdominal aorta. The abdominal aorta distal to this branch directly bifurcates into iliac iliac arteries without giving an origin to renal or inferior mesenteric artery branches. These vascular abnormalities lead to vitelline artery steal of the blood supply to the caudal end of embryo, which leads to sirenomelia and associated anomalies[5]. At blastogenesis, damage to the caudal mesoderm of the embryo between day 13 and day 22 of life results in merging, malrotation, and dysgenesis of the lower extremities.

A diagnosis of sirenomelia may be easier to make during the first trimester because the amniotic fluid volume is relatively normal, because amniotic fluid is secreted by the amniotic

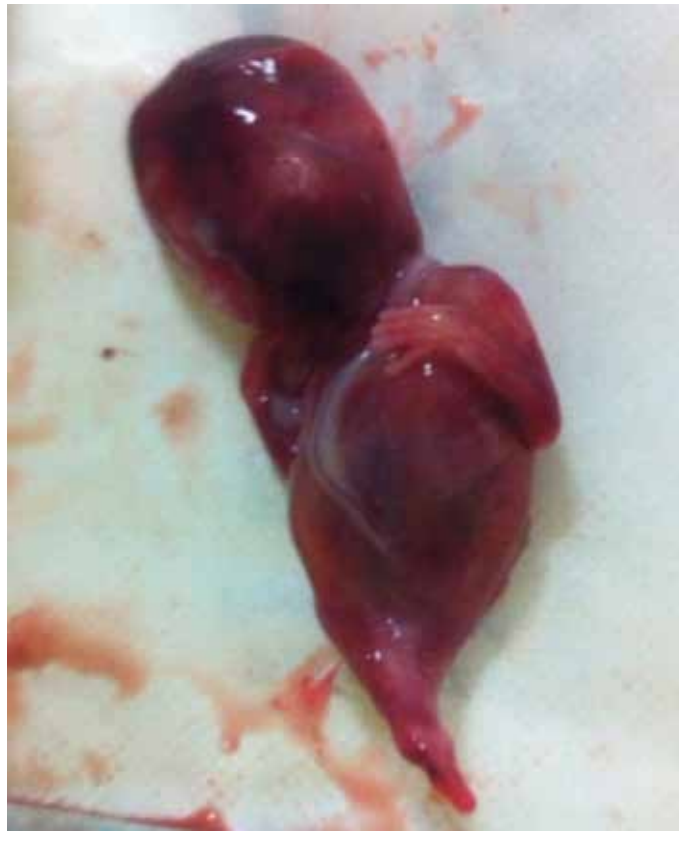

Figure 3. Examination of the fetus

membrane in the first trimester[6]. A diagnosis of sirenomelia is made in early pregnancy through confirmation of the existence of a single lower extremity. At later periods of pregnancy, ultrasonographic diagnosis of sirenomelia may be prevented by severe oligohydramnios due to renal agenesis or dysgenesis. Our patient was referred to us late in the first trimester.

Ethics

Informed Consent: A consent form was filled out by all participants.
Peer-review: Externally peer-reviwed.

Authorship Contributions

Surgical and Medical Practices: Yasemin Doğan, Yasin Ceylan, Concept: Yasin Ceylan, Yasemin Doğan, Design: Yasemin Doğan, Data Collection or Processing: Yasin Ceylan, Analysis or Interpretation: Yasin Ceylan, Sebiha Özkan Özdemir, Literature Search: Yasin Ceylan, Gülseren Yücesoy, Writing: Yasin Ceylan.
Conflict of Interest: No conflict of interest was declared by the authors.
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A 27-kg mucinous cystadenoma of the ovary presenting with deep vein thrombosis

Derin venöz trombozla prezente olan 27 kg'lik overyan müsinöz kistadenom

Esra Nur Tola[1], Evrim Erdemoğlu[2], Yakup Yalçın[2], Filiz Alkaya Solmaz[3], Ebru Erdemoğlu[4]

[1]*Süleyman Demirel University Faculty of Medicine, Department of Gynecology and Obstetrics, Isparta, Turkey*

[2]*Süleyman Demirel University Faculty of Medicine, Department of Gynecologic Oncology, Isparta, Turkey*

[3]*Süleyman Demirel University Faculty of Medicine, Department of Anestesiology and Reanimation, Isparta, Turkey*

[4]*Şifa Hospital, Clinic of Gynecology and Obstetrics, Isparta, Turkey*

Abstract

Giant ovarian adenomas are rarely observed today because of early diagnosis and treatment. Mucinous cystadenomas is a kind of tumor that mostly causes the ovary to enlarge. Theu can present with various and non-specific clinical manifestations such as deep vein thrombosis. The primary symptoms of giant ovarian tumors are abdominal enlargement and distension. Therefore, making the correct preoperative diagnosis is sometimes difficult. The appropriate treatment must include oncologic procedures and a multidisciplinary approach to minimalize complications and save the patient's life.
Herein, we report a woman aged 53 years with a 27-kg ovarian mucinous cystadenoma that presented as a left popliteal vein thrombosis.
Keywords: Abdominal enlargement, deep vein trombosis, giant ovarian tumour, ovarian mucinous cystadenoma

Öz

Günümüzde erken tanı ve tedaviden dolayı büyük overyan adenomlar nadir görülmektedir. Müsinöz kistadenomlar, overi en çok büyüten tümörlerdir. Derin venöz tromboz gibi çok çeşitli ve non-spesifik klinik manifestasyonları olabilir ve major semptomu abdominal genişleme ve distansiyondur. Bu yüzden preoperatif doğru tanı koymak bazen zor olabilir. Hastanın hayatını kurtarmak ve komplikasyonları azaltmak için tedavi onkolojik prosedürleri içermeli ve multidisipliner bir yaklaşım olmalıdır. Burada, sol popliteal venöz trombozu ile gelen 27 kg overyan müsinöz kistadenomlu 53 yaşında bir hastayı sunuyoruz.
Anahtar Kelimeler: Abdominal genişleme, derin venöz trombozu, büyük overyan tümör, overyan müsinöz kistadenom

Introduction

Giant ovarian tumours are now a rare condition because of early diagnosis and treatment. Mucinous cystadenoma (MCA), a tumor that causes ovaries to enlarge, accounts for about 15% of all ovarian neoplasms[1,2]. About 80% of mucinous tumors are benign and are common usually between the third and sixth decade of life[2,3]. Mucinous tumors are usually unilateral and can exceed 30 cm in diameter[4]. Although prognosis is very good, the clinical signs and symptoms of ovarian masses are generally nonspecific. Therefore, making the correct preoperative diagnosis is sometimes difficult, and early management may be necessary to save the patient's life. The purpose of this case was to report a 27-kg ovarian MCA that presented as deep vein thrombosis (DVT).

Case Report

The patient was a woman aged 53 years with an abdominal mass that caused left popliteal and femoral vein thrombosis. She claimed stepwise enlargement of the abdomen and initially thought she had put on weight. However, when swelling progressed in her left leg, she was admitted to an internal medicine clinic. Her condition was diagnosed as DVT and she was referred to us upon finding an abdominal mass in her abdominal ultrasound (USG) examination. Abdominal enlargement and distension were observed, and abdominal USG revealed a 40×50 cm abdominopelvic mass, probably

Address for Correspondence/Yazışma Adresi: Esra Nur Tola, MD,
Süleyman Demirel Univercity Faculty of Medicine, Department of Gynecology and Obstetrics, Isparta, Turkey
Phone: +90 246 211 92 41 **E-mail:** perinatalog@hotmail.com
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originating from her left ovary, with multiple septations and solid areas. Tumor markers (CA 19-9, CA 125) were within the normal range. A malignant ovarian tumor was initially suspected because of the size, and a positron-emission tomography-computerized tomography (PET-CT) was performed. The PET-CT revealed an enormous heterogenic mass with low metabolic activity in the left ovary, a 5×5 cm mass in the right ovary, and bilateral urinary stasis. A laparotomy with midline incision revealed a smooth-surfaced mass that filled the entire abdomen originating from the left ovary and confirmed the 5×5 cm mass in the right ovary (Figure 1). A detailed pelvic examination was performed because of the risk of borderline potential, and it did not indicate metastases. There was minimal free fluid in the pouch of Douglas. The patient had hypotension and bradycardia, and we quickly decided to operate in the lateral position to prevent hemodynamic derangements. The ovarian masses were sent for frozen sectioning. A hysterectomy and bilateral salpingo-oophorectomy was performed because of the giant size of the cystic mass, the presence of a contralateral ovarian mass, and the patient's age. The cystic mass weighed 27 kg. The masses were diagnosed as benign ovarian MCA.

Discussion

Giant ovarian cystadenomas are rarely observed today because of improved imaging techniques[5]. Further, most ovarian cyst adenomas are epithelial cystadenomas, of which 25% are mucinous[6]. MCAs mainly occur during middle age, as in our case, and they are rare among adolescents. There was, however, a report of an ovarian MCA in a premenarchal girl[6]. MCAs are usually unilateral, and are bilateral in 10% of cases (as in our case)[1,7]. MCAs can reach large sizes even though they do not have the potential for malignancy[1,3,8]. The largest reported adnexal cyst was 148 kg[9]. The mass in our patient weighed 27 kg.

In general, MCAs can be found incidentally in routine USG screenings; abdominal enlargement and distension are major symptoms. The most frequent complications are torsion, pressure to the adjacent structures like the viscera, which accounts for urinary stasis and rupture, and spilling of tumor into the peritoneum, known as pseudomyxoma peritonei[7]. In literature, there is no information about an ovarian mass presenting as DVT due to femoral vein pressure.

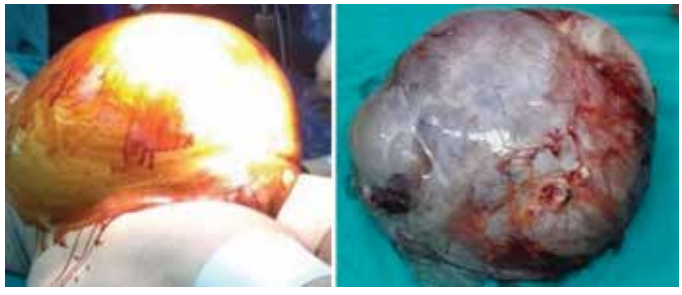

Figure 1. Massive distension of abdomen and giant mucinous ovarian cystadenoma

Ultrasonographic examination of ovarian cysts can exclude malignancy. In most cases, USG examination can reveal a complex adnexal mass, as in our case. When there is a diagnostic doubt, a CT or magnetic resonance imaging scan is performed. In our case, PET-CT scan was performed because of a suspicion of malignancy. Although tumor markers can identify cyst characterization in most instances, they are more important in monitoring postoperative relapse[6].

Large ovarian cysts traditionally require laparotomy because of their size[10]. Cystectomy cannot be performed because of the absence of normal tissue; adnexectomy is the classic treatment. If there is a suspicion of malignancy, a laparotomy with oncologic procedures is recommended[7]. Although some studies suggest laparoscopy, there are still debates because of tumor size limitations[10]. We preferred laparotomy owing to the tumor dimension and suspicion of malignancy[2,5].

Giant ovarian cysts have significant morbidity if not managed properly. A multidisciplinary approach must be taken preoperatively. Giant ovarian cysts can cause hemodynamic and pulmonary complications; therefore, central venous pressure monitorization is recommended during operations. The lateral decubitus position is preferred during the operation.

Conclusion

MCAs can present as different clinical conditions such as DVT. The appropriate treatment must include oncologic procedures, and a multidisciplinary approach must be undertaken to minimalize complications.

Ethics

Informed Consent: Consent form was filled out by all participants.
Peer-review: Internal and Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Esra Nur Tola, Evrim Erdemoğlu, Yakup Yalçın, Filiz Solmaz, Concept: Esra Nur Tola, Ebru Erdemoğlu, Design: Esra Nur Tola, Data Collection or Processing: Esra Nur Tola, Analysis or Interpretation: Esra Nur Tola, Literature Search: Esra Nur Tola, Writing: Esra Nur Tola, Evrim Erdemoğlu.
Conflict of Interest: No conflict of interest was declared by the authors.
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