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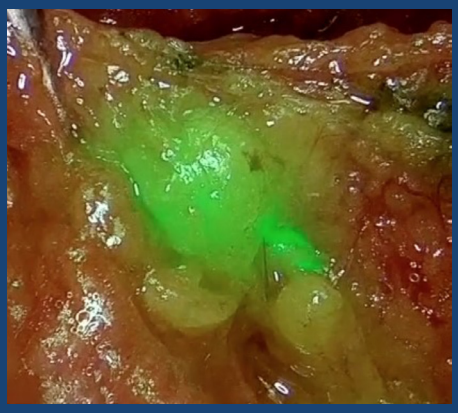

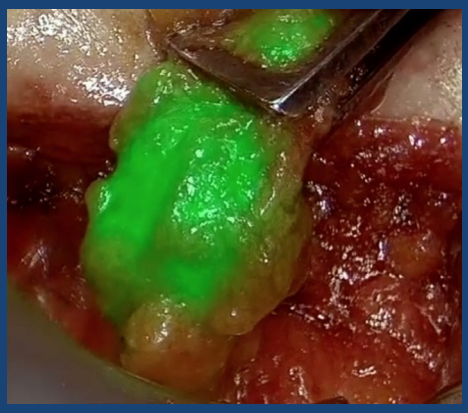

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Cover Picture: Wunster et al. Inguinal sentinel lymph node in vulvar carcinoma

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Aims and Scope

Journal of the Turkish-German Gynecological Association is the official, open access publication of the Turkish-German Gynecological Education and Research Foundation and Turkish-German Gynecological Association and is published quarterly on March, June, September and December. The publication language of the journal is English. Manuscripts are reviewed in accordance with "double-blind peer review" process for both reviewers and authors.

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The ''Journal of the Turkish-German Gynecological Association'' (EISSN 1309-0380; Abbreviated as "J Turk Ger Gynecol Assoc") is the official, open access publication of the Turkish-German Gynecological Education and Research Foundation and the Turkish-German Gynecological Association. Formerly named "ARTEMIS", the journal is published quarterly (March, June, September, December) in English and publishes original peer-reviewed articles, reviews, and commentaries in the fields of Gynecology, Gynecologic Oncology, Endocrinology & Reproductive Medicine and Obstetrics. Case reports are not accepted for publication. Reviews will be considered for publication only if they are prepared by authors who have at least three published manuscripts in international peer reviewed journals and these studies should be cited in the review. Otherwise only invited reviews will be considered for peer review from qualified experts in the area.

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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/),

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

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

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

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Present the detailed findings supported with statistical methods. Figures and tables should supplement, not duplicate the text; presentation of data in either one or the other will suffice. Emphasize only your important observations; do not compare your observations with those of others. Such comparisons and comments are reserved for the discussion section.

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Contents

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Editorial

Dear Colleagues,

It is my great pleasure to introduce the second issue of the "Journal of the Turkish-German Gynecological Association (J Turk Ger Gynecol Assoc)" in the publishing year of 2024. This issue is consisted of seven articles and one review that we hope you will read with interest. Also you may have the oppurtunity to read the letters to the editor. Here we share some of our favorite articles that were published in this issue of the journal.

Worldwide, polycystic ovarian syndrome (PCOS) is a common endocrine disorder among people of reproductive age. Increased levels of luteinizing hormone (LH) are frequently linked to PCOS, and this may have an impact on oocyte quality by promoting hyperandrogenism. You will read an article evaluating the impact of LH stimulation on IVF cycle outcomes in patients with PCOS.

Cytological specimens that do not fit the requirements for a high grade squamous intraepithelial lesion (HSIL) are categorized as "atypical squamous cells, cannot exclude high grade squamous intraepithelial neoplasia (ASC-H)" in the Bethesda 2014 classification. It is believed that in cases of HPV positive ASC-H, the prevalence of cervical intraepithelial neoplasia 2+ (CIN 2+) lesions ranges from 30% to 47%. However, there is little information in the literature currently in publication about the relationship between HPV subtypes and the probability of CIN 2+ lesions in ASC-H cytology. You will also read an article which assesses the correlation between CIN 2+ lesions and high-risk HPV subtypes among patients who presented with HPV-positive ASC-H cytology.

You will also have the opportunity to read a review discussing practical overview of management of postmenopausal endometriotic symptoms, use of hormone replacement therapy in postmenopausal women with a history of endometriosis and future risk of malignancy.

Dear Participants,

I would like to invite you to join us for our "Symposium on Current Approaches in Obstetrics and Gynecology", which will be held in İstanbul on May 31-June 1 2024. The scientific programme of the symposium includes many distinguished scientists and researchers both from Turkey and Europe.

Additionally, I would like to remind you that our esteemed 15th Turkish-German Gynecology Congress, scheduled for April 23-April 27, 2025, in Antalya, is quickly coming. As previously said, our congress will be conducted in accordance with the strictest scientific guidelines, and we are constantly striving to enhance our conventional congress.

Dear Esteemed Readers,

Our published articles cover a wide range of obstetrics and gynecological topics. As can be seen, JTGGA is seeing a rise in citation counts as well. The utilization of keywords in the title, presentation of the study at conferences, use of the same form for your name and surname, sharing of your data on social media, and key word selection will all contribute to a higher number of citations. I would like to use this chance to express our gratitude to everyone who has supported our journal. We are appreciative to our readers, reviewers, and writers.

Please visit us online at www.jtgga.org and keep in touch with us by following us on Twitter @JtggaOfficial.

We are looking forward to receiving your valuable submissions, thank you in advance for your contributions.

Sincerely,

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

Impact of stimulation with luteinizing hormone activity on IVF outcomes in patients with polycystic ovary syndrome

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The first two authors had equal contribution

Abstract

Objective: To compare in-vitro fertilization (IVF) outcomes in polycystic ovary syndrome (PCOS) patients treated with follicle stimulating hormone (FSH) alone or FSH and luteinizing hormone (LH), under freeze-all gonadotropin-releasing hormone (GnRH) antagonist protocols.

Material and Methods: This retrospective study at a university center included PCOS patients, who underwent freeze-all GnRH antagonist IVF cycles between January 2013 and December 2019. They were divided into FSH-only and FSH + LH groups, focusing on pregnancy and live birth rates.

Results: The study included 82 patients: 43 received FSH + LH and 39 FSH only. Baseline characteristics were similar, except for higher thyroid stimulating hormone levels in the FSH-only group. The FSH + LH group required a lower mean ± standard deviation total dose of FSH (1271.5±376.7 vs. 1407.2±645.3 IU, p=0.02), had a shorter mean cycle length (7.3±3.4 vs. 8.3±1.6 days, p=0.004), and had a higher mean number of follicles stimulated (36.9±15.9 vs. 35.9±9.7, p=0.008) compared to the FSH-only group. No significant differences in pregnancy and live birth rates were noted at first transfer, but the cumulative live birth rate was significantly higher in the FSH-only group [30 of 39 (76.9%) vs. 24 of 43 (55.8%), p=0.044].

Conclusion: LH supplementation in PCOS patients undergoing GnRH antagonist IVF protocols may impair cumulative live birth rates, despite lowering FSH requirement and reducing IVF cycle length. These results highlight the complex role of LH in IVF outcomes for PCOS patients, suggesting a need for further large studies to fully understand the impact of LH in such treatments. (J Turk Ger Gynecol Assoc 2024; 25: 60-5)

Keywords: Polycystic ovary syndrome, fertilization in vitro outcome, luteinizing hormone treatment, ovarian stimulation

Received: 10 January, 2024 **Accepted:** 22 March, 2024

Introduction

Polycystic ovary syndrome (PCOS) is a prevalent condition in reproductive-age patients globally, with symptoms that vary, influencing its reported prevalence (1). Patients with PCOS exhibit increased luteinizing hormone (LH) pulsatility, characterized by more frequent pulses in all subjects and heightened amplitude, particularly in lean individuals (2). Elevated LH levels promote hyperandrogenism by stimulating theca cells, leading to increased intra-ovarian androgen levels (3). This hormonal imbalance, along with heightened serum LH, may contribute to disrupted granulosa cell function, increased oocyte atresia, and premature maturation of oocytes (4).

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In patients with PCOS undergoing in-vitro fertilization (IVF), concerns regarding oocyte quality and its impact on fertilization rates and outcomes have been noted (5). A previous study indicated that patients with PCOS experienced lower live birth rates per fresh embryo transfer compared to patients with normal ovulation and without PCOS (6).

The hypothesis that LH or LH activity in IVF stimulation could potentially lead to less favorable outcomes than follicle stimulating hormone (FSH) alone in patients with PCOS is based on the fact that PCOS is often associated with elevated LH levels, which can promote hyperandrogenism and potentially affect oocyte quality (3). Studies, including those by Singh et al. (7) and Sun et al. (8), have explored the role of high basal serum LH levels in PCOS on IVF outcomes, but these investigations found no significant differences in critical outcomes, such as clinical pregnancy and live birth rates. This suggests that the relationship between LH levels and IVF success in PCOS patients might be more complex than previously thought. However, it's important to note that basal LH levels can fluctuate in a pulsatile manner (9) and may not fully represent a patient's clinical status. To address this, the aim of our study was to specifically evaluate the impact of LH stimulation on IVF cycle outcomes in patients with PCOS.

Material and Methods

This was a retrospective cohort analysis at a single university center. It included patients treated between January 2013 and December 2019 who were diagnosed with PCOS based on the Rotterdam consensus criteria (10). The study focused on those who underwent freeze-all gonadotropin-releasing hormone (GnRH) antagonist IVF cycles, comparing outcomes between those who received FSH alone and those who received FSH combined with LH activity. In our study, LH activity was induced by administration of human chorionic gonadotropins (hCG) added to human menopausal gonadotropins (hMG) (Ferring Canada, Montreal, Canada), or as recombinant Lutropin-alpha (Merck Serono, Montreal, Canada).

The study was submitted and approved by the board of the McGill University Research Ethics Office (Internal Review Board) of the Faculty of Medicine and Health Sciences (approval number: 2020-5971).

In this study, PCOS was defined according to the 2003 Rotterdam criteria, which include any two of the following three features: oligo- or anovulation, signs of hyperandrogenism (either clinical or laboratory-based), and ultrasound evidence of polycystic ovaries, while ruling out other etiologies (10).

The study focused on patients undergoing freeze-all GnRH antagonist IVF cycles, specifically comparing the effects of FSH alone versus a combination of FSH and LH stimulation. This approach was chosen to isolate the impact of LH on the oocyte-follicle complex, eliminating potential LH effects on the endometrium. All eligible patients within the study period were included in the analysis.

For comprehensive data analysis, various factors were reviewed: patient age, gravida, parity, male partner's age, duration of infertility, basal levels of FSH, LH, estradiol, prolactin, thyroid stimulating hormone (TSH), total and free testosterone, and basal antral follicle count, along with sperm parameters, such as volume, concentration, and motility. This allowed for a detailed assessment of the influence of LH stimulation on IVF outcomes in the context of PCOS.

We excluded patients who did not meet the Rotterdam criteria for PCOS. In addition, we disregarded cases with incomplete cycle information (n=7), specifically those lacking details on secondary and primary outcomes. We also chose to exclude IVF cycles that resulted in fresh-embryo transfers. Furthermore, patients with untreated intra-cavity pathologies, such as fibroids or polyps, as well as males with severe male factor infertility (defined as less than 5 million total motile sperm count), were not included in the analysis.

Ovarian stimulation in our study was conducted using either recombinant follicle stimulating hormone (rFSH) (Follitropin Alpha by Merck Serono, Montreal, Canada, or Follitropin Beta by Organon, London, Canada), hMG (Menopur by Ferring, Montreal, Canada), or recombinant LH (Lutropin Alpha by Merck Serono, Montreal Canada). This began on day 3 of a fixed start antagonist protocol. The GnRH antagonist (either Cetrotide by Merck, Kirkland, Canada or Orgalutran by Organon, Kirkland, Canada) was introduced on cycle day 6. A normal baseline transvaginal ultrasound on day 2 or 3, confirming the absence of functional ovarian cysts, was a prerequisite for initiating IVF stimulation. The decision to add LH activity varied according to physician preference and was based on a combination of factors including patient age, ovarian reserve, previous response to stimulation, and specific clinical indications, aiming for a personalized treatment approach within the framework of the study.

Follicle monitoring via ultrasound commenced on cycle day 7 and was then adjusted based on ovarian response. 1000 IU subcutaneous injection of Buserelin (Sanofi-Aventis, North York, Canada) was used as a GnRH agonist for follicular maturation, and oocyte retrieval occurred 36 hours post-administration. Intracytoplasmic sperm injection (ICSI) was performed in cases of poor motility (<30%), and abnormal morphology, and after unsuccessful fertilization in previous IVF attempts without ICSI. All cycles in this study were freeze-all, with embryos being transferred in subsequent cycles.

The primary outcomes of the study were pregnancy and live birth rates. The pregnancy rate was determined by a positive serum hCG level of over 10 IU/L, measured 16 days after the

frozen embryo transfer. The clinical pregnancy rate is defined by ultrasound evidence of a gestational sac, embryo, and fetal heartbeat at 6 to 7 weeks of gestation. The live birth rate indicates a live child's birth after 24 weeks of gestation. Cumulative rates consider all outcomes from a single IVF cycle's embryos, with the clinical rate including early pregnancies confirmed by ultrasound and the live birth rate encompassing all live births from the cycle's embryos until they are fully utilized or result in a conception.

The study's secondary outcomes pertained to various elements of the IVF stimulation process, including the length of the IVF cycle, the total amount of gonadotropins administered, the highest estradiol level recorded during stimulation, and the maximal endometrial thickness observed on the day of ovulation induction. In addition, we assessed the total number of oocytes retrieved, the count of mature (MII) oocytes, the number of embryos that developed to the 2 pronuclei stage (2PN), and the total number of blastocysts that were cryopreserved. For cryopreservation, blastocysts were selected based on a minimum quality threshold defined by Gardner's grade (11), with BB or higher being the standard for freezing.

The study's results were reported in accordance with the STROBE guidelines.

Statistical analysis

Data in the study were processed using SPSS version 28.0 (IBM Corporation, Chicago, IL, USA). Data was assessed for normal distribution employing the Kolmogorov-Smirnov test and it was found that the continuous data was normally distributed. Baseline characteristics of the patients were then described using means, standard deviations, and ranges or percentages, as appropriate.

For the primary and secondary outcomes, t-tests were used for analysis, applying Levene's test to ensure equality of variances. Significance was determined with a two-tailed p-value, setting the threshold for statistical significance at less than 0.05.

Results

Our study included 82 patients who met the inclusion criteria. Of these, 43 were administered both FSH and LH activity, while the remaining 39 received only FSH. The baseline characteristics of both groups were comparable, with the notable exception of initial serum TSH levels. The group receiving only FSH exhibited higher pre-treatment serum TSH levels (average 3.6±8.3 mU/L) compared to the FSH and LH group (1.8±1.0 mU/L), a difference that closely approached significance (p=0.05). For participants with TSH levels above 3.5 mU/L, levothyroxine was administered to reduce serum TSH to below 2.0 mU/L prior to initiating the IVF cycle. Baseline characteristics are presented in Table 1.

There were no significant differences in several IVF outcomes between the FSH alone and FSH + LH groups. These outcomes included the pregnancy rates, clinical pregnancy rates, and live birth rates after the first embryo transfer, as well as the cumulative pregnancy rates.

Table 1. Patient baseline characteristics in the treatment groups

Variable	FSH and LH, (n=43)	FSH only, (n=39)	p
Gravidity	0.6±1.1	0.6±0.8	0.129
Parity	0.2±0.4	0.3±0.6	0.063
Female age (years)	30.8±2.8	30.2±3.6	0.345
Male age (years)	33.9±5.0	35.7±6.8	0.247
Duration of infertility (years)	3.0±2.2	3.3±2.5	0.607
Basal serum FSH (IU/mL)	6.1±1.7	5.5±1.5	0.980
Basal serum LH (IU/L)	9.4±6.7	7.8±5.2	0.454
Basal serum estradiol (pmol/L)	247.5±349.9	216.4±146.6	0.560
Basal serum prolactin (μg/L)	10.4±5.4	10.8±4.3	0.639
Basal serum TSH (mU/L)	1.8±1.0	3.6±8.2	0.05
Basal total serum testosterone (nmol/L)	1.9±1.2	1.4±0.7	0.098
Basal free serum testosterone (nmol/L)	0.8±0.6	0.6±0.4	0.212
AFC	45.9±1.3	44.6±17.3	0.856
Sperm volume (mL)	2.9±1.3	2.6±1.4	0.671
Sperm concentration (millions/mL)	44.8±39.2	35.7±32.3	0.265
Sperm motility (%)	44.3±23.7	38.2±30.2	0.038

Data are presented as mean ± standard deviation. FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, TSH: Thyroid stimulating hormone, AFC: Antral follicle count

However, an interesting observation was the difference in cumulative live birth rate, which was higher in the FSH-only group (30 of 39, 76.9%) compared to the FSH + LH group (24 of 43, 55.8%), a difference that reached significance (p=0.044) (Table 2).

There were no significant differences in most stimulation outcomes. Specifically, peak serum estradiol, peak endometrial thickness, the number of oocytes collected, MII oocytes, 2PN embryos, and blastocysts frozen showed comparable results between the two groups (Table 3).

However, the FSH + LH group required a lower total dose of FSH (1271.5±376.7 vs. 1407.2±645.3 IU, p=0.02), had a shorter IVF cycle stimulation length (7.3±3.4 vs. 8.3±1.6 days, p=0.004), and had a higher number of follicles stimulated (36.9±15.9 vs. 35.9±9.7 p=0.008) compared to the FSH-only group (Table 3).

Discussion

In this study comparing IVF cycles among PCOS patients undergoing freeze-all GnRH antagonist protocols, no significant differences were found in initial and cumulative pregnancy rates, clinical pregnancy rates, and live birth rates between patients treated exclusively with FSH and those receiving a combination of FSH and exogenous LH. However, the cumulative live birth rate was higher in the FSH-only group compared to the combined FSH + LH group. The combined treatment group, however, required lower total doses of FSH, had shorter cycle durations, and achieved a higher number of stimulated follicles than the FSH-only group.

No significant differences were found in most measures, such as total oocytes collected, number of mature (MII) oocytes, fertilization rate, and embryos frozen. Similarly, primary outcomes, like cumulative pregnancy rates, first transfer pregnancy and clinical pregnancy rates, and live birth rates after the first transfer showed no statistical differences. However, cycle length and total follicles were notably different, with the FSH plus LH group showing advantages. This aligns with the known effect of LH on theca cells, stimulating small follicle growth (12,13). Despite more follicles, the addition of LH appeared to adversely affect oocyte quality, as suggested by lower cumulative live birth rates in this group. Previous studies have not directly compared rFSH alone versus rFSH with LH supplementation in GnRH antagonist cycles in PCOS patients. However, the effect of elevated basal LH/FSH ratios on IVF stimulation cycles has been explored. Singh et al. (7) conducted a retrospective cohort study examining the influence of high basal day 2 or 3 LH levels and LH:FSH ratio on IVF cycle outcomes in PCOS patients. They reviewed 164 cycles and found that those with lower basal LH levels showed higher fertilization rates and a greater number of fresh embryo transfers (7). Furthermore, Wang et al. (14) observed significant differences in cumulative clinical pregnancy rates

Table 2. Pregnancy outcomes

Variable	FSH and LH, (n=43)	FSH only, (n=39)	p
Pregnancy rate at the first transfer (%)	22 (51.2)	23 (59.0)	0.478
Clinical pregnancy rate after the first transfer (%)	16 (37.2)	18 (46.2)	0.412
Live birth rate following first transfer (%)	10 (23.3)	15 (38.5)	0.135
Cumulative clinical pregnancy rate (%)	32 (74.4)	33 (84.6)	0.441
Cumulative live birth rate (%)	24 (55.8)	30 (76.9)	0.044
FSH: Follicle-stimulating hormone, LH: Luteinizing hormone			

Table 3. Cycle characteristics and IVF stimulation outcomes

Variable	FSH and LH, (n=43)	FSH only, (n=39)	p
Cycle length (days of FSH stimulation)	7.3±3.4	8.3±1.6	0.004
Total dose of FSH (IU)	1407.2±645.3	1271.5±376.7	0.020
Peak serum estradiol (pmol/L)	13231±6859	11716±5086	0.220
Endometrial thickness (mm)	10.2±1.8	10.4±2.4	0.257
Total follicles stimulated (at least 10 mm)	36.9±15.9	35.9±9.7	0.008
Oocytes collected	27.0±9.4	28.4±9.7	0.837
Number of MII oocytes	20.0±7.9	21.6±8.2	0.861
Number of 2PN embryos	14.7±7.7	16.7±7.1	0.986
Number of embryos frozen	7.9±4.9	7.7±5.03	0.571
Data are presented as mean ± standard deviation. IVF: In-vitro fertilization, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, MII oocytes: Mature oocytes, 2PN: 2 pronuclei stage			

in PCOS patients undergoing GnRH antagonist IVF cycles, based on varying basal serum LH levels on the day of hCG trigger. Their study suggested that increasing LH levels during ovarian hyperstimulation could detrimentally affect pregnancy outcomes, possibly through adverse effects on oocytes, embryos, or the endometrium (14). Although baseline TSH levels were elevated in the FSH-only group, these levels were normalized before beginning the IVF cycle.

LH plays a crucial role in follicular recruitment, including stimulating FSH receptor expression in granulosa cells, facilitating follicular maturation, and promoting embryo implantation by affecting endometrial stromal cells (3). Its importance is evident in patients with hypogonadotropic hypogonadism (HH), where LH supplementation has shown benefits in ovarian stimulation. It has been found that HH patients treated with HMG, which contains LH activity, required lower FSH doses and achieved better ovulation rates and endometrial development compared to those treated with FSH alone (15). However, there is a balance to be maintained, as excessive LH activity can lead to premature follicular maturation and atresia. High serum LH levels during the follicular phase are associated with poorer oocyte quality, reduced fertilization rates, impaired embryo implantation, and increased miscarriage risks (16). This may explain the higher cumulative live birth rate that was observed in the FSH-only group.

Previous studies (12,17) have explored ovarian stimulation protocols in non-PCOS subjects, but the present study is unique in its focus on PCOS patients under GnRH antagonist protocols. Furthermore, it is important to acknowledge the distinct effects of long GnRH agonist and GnRH antagonist protocols on endogenous LH levels in IVF. Long GnRH agonist cycles typically lead to a significant reduction in serum LH levels in PCOS patients, potentially extending over three to four weeks, starting from pre-stimulation. In contrast, GnRH antagonist protocols cause a more transient suppression of LH, often lasting only a few days (18,19). This difference in LH dynamics may result in varying IVF outcomes, especially for PCOS patients. The rationale for using GnRH antagonist protocols, for reducing ovarian hyperstimulation syndrome risk, is well-established (20). The results of the present study suggest that LH supplementation may have varying effects in PCOS patients, who naturally exhibit elevated endogenous LH levels. These levels could be further amplified in patients undergoing GnRH antagonist protocols, underscoring the need for careful consideration of LH supplementation in this specific patient group.

The higher cumulative live birth rate observed in the FSH only group, as opposed to the FSH with LH activity group, could be attributed to the exclusive focus on PCOS patients. Elevated LH concentrations in these patients may negatively impact oocyte quality, as inferred from live birth potential. Furthermore, patients with high basal LH levels are likely to exhibit elevated progesterone levels on IVF trigger days, potentially affecting oocyte potential, even in frozen cycles (7).

Study limitations

The findings of this study are innovative, yet they are subject to certain limitations that warrant attention. The retrospective design and limited sample size could introduce confounding factors, possibly affecting the interpretability of the results. A larger sample might reveal statistical significance in cumulative pregnancy rate and other primary outcomes. Nevertheless, the observed clinical outcomes are significant enough to merit reporting. Due to the scale of the study, it should primarily serve as a basis for hypothesis generation, with further validation required from larger-scale studies. While we inferred improved oocyte quality from better clinical outcomes, this was not directly measured. In addition, the impact of the timing of exogenous LH addition, which in this study coincided with FSH stimulation, may influence oocyte maturation and clinical results. Different outcomes might have been observed if LH stimulation had been administered only during the late follicular phase.

Conclusion

This study found that for PCOS patients undergoing GnRH antagonist IVF “freeze-all” protocols, ovarian stimulation with FSH and LH resulted in comparable clinical pregnancy and live birth rates to using FSH alone. However, FSH and LH stimulation allowed for reduced FSH dosages, a shorter duration of IVF stimulation, and an increased number of stimulated follicles, when compared to FSH alone. Despite these benefits, the cumulative live birth rate was lower with FSH and LH stimulation when compared to treatment with FSH only.

Ethics Committee Approval: *The study was submitted and approved by the board of the McGill University Research Ethics Office (Internal Review Board) of the Faculty of Medicine and Health Sciences (approval number: 2020-5971).*

Informed Consent: *Retrospective study.*

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Exploring the role of SOX 2 and OCT 4 in the pathogenesis of gliomatosis peritonei: the clinicopathological profile of eleven cases

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Abstract

Objective: Gliomatosis peritonei (GP) is a rare entity characterized by multiple mature glial tissue implants in association with ovarian teratomas in the peritoneum and omentum. To date, only 100 cases have been published. Not much is known about the origin, clinicopathological profile or prognosis of GP. SOX2 and OCT4 are recently recognized markers of embryonic stem cell differentiation. Here, the role of SOX2 and OCT4 in the pathogenesis of 11 cases of GP are reported and clinicopathological factors are described.

Material and Methods: This was a retrospective study of six years duration (2017-2022). All the cases of GP were retrieved from archives, the diagnosis was confirmed and clinicopathological factors were noted. Immunohistochemical (IHC) investigation for glial fibrillary acid protein (GFAP) and S100 was noted wherever available. IHC for SOX2 and OCT4 was performed using an avidin-biotin technique.

Results: There were 11 cases of GP identified. The median age was 29 years and 1/11 cases had nodal gliomatosis as well. There were eight cases of immature teratoma and three cases of mature cystic teratoma. SOX2 was positive in all foci of GP, while OCT4 was negative. These foci were also positive for GFAP and S100.

Conclusion: A possibility of GP should be considered as a differential, clinically and radiologically, in cases of omental nodularity. Adequate sampling at the time of surgery is essential to rule out metastasis or growing teratoma syndrome. SOX2, a stem cell marker inducing neural differentiation, may play a crucial role in the development of GP in association with other transcription factors. (J Turk Ger Gynecol Assoc 2024; 25: 66-73)

Keywords: Ovary neoplasm, teratoma, gliomatosis peritonei, SOX2, omental glial implants, malignant transformation, mature cystic teratoma, growing teratoma syndrome

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Introduction

Gliomatosis peritonei (GP) is a rare entity characterized by multiple mature glial implants in the peritoneum and omentum. It is associated with teratomas, usually immature teratoma (IMT), in most of cases. To date only 100 cases have been reported (1). According to the World Health Organization (WHO) guidelines for grading IMT, this tumor is graded as grade 0 and is thought to have good prognosis wherever found. However, due to the rarity of this disease, there is little data pertaining to its clinicopathological characteristics. Moreover, the origin of GP is still ambiguous. Recent studies of stem cell differentiation have demonstrated that OCT4 (Pou5f1-POU domain, class 5, transcription factor 1) and SOX2 (SRY-box containing gene 2), in conjunction with other transcription factors, act as master regulators for embryonic stem cell differentiation towards mesoderm (2). Several authors have demonstrated that SOX2 plays a key role in direct reprogramming of human somatic cells into neural progenitor cell types (3). In this study, 11 cases of GP diagnosed and treated at our referral center were retrospectively reviewed

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and the role of SOX2 and OCT4 was investigated in these cases. The currently published literature was also reviewed to add to the understanding of this rare disease.

Material and Methods

Clinical Profile

This was a retrospective study of all cases of GP received at our referral centre in India. Over the last 6 years (2017-2022), 11 cases of GP were identified. The clinical and pathological details of these cases were retrieved from the records and retrospectively reviewed to evaluate the clinicopathological factors, including age, laterality, serum markers, radiological details, nature of primary tumor, morphological features, and complications, if any. The outcomes were noted where available. Cases where sufficient details or histopathology slides were not available were not included in the study. For the purpose of this study, cases where GP was associated with growing teratoma syndrome (GTS), or with a history of prior chemotherapy were excluded. Since this study was performed on retained histopathological samples from the departmental archives, ethics approval was not taken as per our institutional review board guidelines. Descriptive statistics was used and the results were expressed as percentages. Data was analyzed using SPSS software, version 22, wherever needed (IBM Inc., Armonk, NY, USA).

Pathological Profile

Histopathological slides of all cases were reviewed by two pathologists for confirmation of diagnosis of the primary tumor, the amount of mature glial differentiation in the primary tumor (all teratomas), the grade of IMT, stage, presence of metastatic disease and the extent of GP was noted. IMTs were graded as per the published guidelines. All the lymph node slides were reviewed to look for presence of nodal gliomatosis and to exclude coexisting nodal metastasis.

Immunohistochemical Staining

Immunohistochemistry (IHC) for glial fibrillary acid protein (GFAP) and S100 was noted from the records (done as a part of routine diagnostic workup). Paraffin-embedded tissue blocks (n=11) and an unstained, Poly-L-Lysine coated slide, containing GP were used for IHC staining for SOX2 and OCT4. IHC staining for SOX2, using the human monoclonal antibody at 1:100 dilution and pH 9 (Zeta corporation) and OCT4, using a monoclonal antibody at 1:100 dilution and pH6 (Zeta corporation) was performed. The tumor sections were deparaffinized, rehydrated, blocked with endogenous peroxidase blocker at room temperature for five minutes and antigen retrieval was performed using the microwave method. Slides were incubated with primary antibodies overnight at 4 °C, followed by a biotin-labelled secondary antibody for 10 minutes. Following staining with 3,3'-diaminobenzidine chromogen, the sections were counterstained with haematoxylin, dehydrated, and mounted. Appropriate positive controls and negative controls were included in each run. Only nuclear staining for OCT4 and SOX2 was considered to be positive.

Statistical analysis

Descriptive statistics were produced using SPSS, version 22 (IBM Inc., Armonk, NY, USA) and results were calculated as percentages in this study.

Results

A total of 615 ovarian teratomas (OT) were received in the department of pathology in the last six years, of which 472 were mature cystic teratomas (MCT) and 143 were IMT. Only 1.6% (11/615) of all teratomas were associated with GP. One of the patients having GTS with GP was excluded from this study. The clinicopathological details of these 11 patients are summarized in Table 1 and the histopathology review findings are summarized in Table 2. Nearly all the patients presented with a short history (average 1.5 months) of abdominal distention along with complaints of abdominal pain in some. The median (range) age of GP patients was 29 (14-35) years and the median size of primary ovarian tumor was 21.4 (14-29) cm. The tumor was left sided in 6/11 cases, right sided in three and was bilateral in two. The serum CA125 levels, available for four cases, was raised, ranging from 324 to 906 U/mL. While radiological investigations in all cases diagnosed adnexal mass with accuracy, the associated GP nodules were reported as peritoneal/omental deposits or thickening and were misperceived as peritoneal carcinomatosis in 50%, more so with IMT cases.

Grossly, the adnexal masses were predominantly solid cystic with areas of hemorrhage and necrosis in IMT. The omental nodules ranged in size from 0.3 to 0.8 cm in diameter and were grey, and white and homogenous on cut section. On microscopy, a total of 11 teratoma cases were associated with GP, 8/11 of these were IMT and the rest (4/11) were MCT. Of the IMT, 71% (6/8) were grade 3 and 2/8 were grade 2. We did not find any case of low grade IMT (grade 1) associated with GP in this series. Of the four MCTs, one was bilateral in origin, and one coexisted with IMT in the other ovary. Table 2 summarizes the histopathological findings of these cases. It was noted that in all cases, the extent of mature glial differentiation accounted for up to 20% of the primary tumor on average, ranging from 5-45%. Case 5 with bilateral MCT had mature glia in both the tumors, although the one on the left side showed up to 45% of mature glial differentiation with no capsular breach, while the right side exhibited only 15%. Case 11 also showed mature

glial tissue in both ovaries. Capsular breach was noted in 63% (7/11) of cases, including one case of MCT (Case 2). Along with capsular breach, Case 2 also had nodal GP but had no recurrence or metastasis on follow-up. IHC staining for GFAP and S100 as a part of routine diagnostic workup was performed in six cases, all of which demonstrated positive cytoplasmic staining, supporting the diagnosis of GP. Other IHC stains performed included SALL4, pan-cytokeratin and CD99 in Case 6 which were immunonegative on IHC.

IHC for SOX2 and OCT4 was performed to investigate the stem cell origin of GP foci in these cases. It was noted that while 100% (11/11) of these cases showed diffuse nuclear immunopositivity for SOX 2, all were immunonegative for OCT 4 (Figure 1).

Table 1. Clinicopathological features of 11 cases of GP

Case no.	Age	Cl/F	CA125, U/mL	Site	Tm size	Procedure	Diagnosis	Mets/Om	Outcome
1	22	AD*, PA# x 1 m	392	Rt	20	RSO, Om, PLND	IMT grade 3	GP	Alive; 60 months
2	27	AD*, PA# x 2 m	NA	Lt	23	TAH + BSO, Om, PLND, peritonectomy	MCT	GP with nodal GP	Alive at 48 months
3	32	AD* x 3 m	NA	Lt	25	LSO, peritonectomy	IMT grade 3	GP	Alive; 46 months
4	31	AD* x 1 m	367	Rt	23	RSO, Om, POD bx	IMT grade 2	GP	Alive; 38 months
5	23	AD*, PA# x 1 m	324	B/L	20	LSO, Rt cystectomy, Om, peritoneal Bx	B/L MCT	GP	Alive; 24 months
6	30	AD* x 2 m	238	Lt	19	LSO, Om	IMT grade 2	GP	LTFU
7	35	PA#, AD* x 1 yr	NA	Rt	29	TAH, BSO, Om	MCT	GP	Alive; 15 months
8	34	AD* x 3 m	NA	Lt	14	TAH BSO, Om	IMT grade 3	GP	LTFU
9	27	AD* x 1 m	906	Lt	17	LSO, Om, peritoneal Bx	IMT grade 3	GP	Alive; 14 months
10	14	AD*, PA# x 1 m	NA	Lt	24	LSO, Om, peritoneal Bx	IMT grade 3	GP	Alive; 6 months
11	30	AD* x 3 m	NA	Rt	24	RSO, Lt cystectomy, Om	IMTgrade 3 Rt MCT Lt	GP	Alive at 3 months

*AD: Abdominal distention, #PA: Pain abdomen, IMT: Immature teratoma, MCT: Mature cystic teratomas, GP: Gliomatosis peritonei, Rt: Right, Lt: Left, Om: Omentectomy, RSO: Right salpingoophrectomy, LSO: Left salpingoophorectomy, TAH: Total abdominal hysterectomy, BSO: Bilateral salpingo-ophrectomy, POD: Pouch of douglas, B/L: Bilateral, PLND: Peritoneal Lymph node dissection, LTFU: Lost to follow-up

Table 2. Histopathological findings in 11 cases of GP

Case	Diagnosis	Grade	Morphology (%) of mature glia in the tumor	Capsular breach	Metastasis	IHC GFAP	IHC S100	IHC SOX2	IHC OCT4
1	IMT	3	10-20%	No	No	NA	NA	+	-
2	MCT		20-30%	+	No	+	NA	+	-
3	IMT	3	10-20%	+	No	+	NA	+	-
4	IMT	2	30-35%	+	No	+	+	+	-
5	B/L MCT		40-45% in Lt and 5-10% in Rt	No	No	+	NA	+	-
6	IMT	2	20-25%	+	No	NA	+	+	-
7	MCT		5-10%	No	No	NA	+	+	-
8	IMT	3	20-25%	+	No	+	+	+	-
9	IMT	3	20-25%	+	No	NA	+	+	-
10	IMT	3	15-20%	+	No	+	+	+	-
11	IMT Rt MCT Lt	3	20-25% in Rt and 10-15% in Lt	No	No	NA	NA	+	-

GP: Gliomatosis peritonei, IHC: Immunohistochemical, GFAP: Glial fibrillary acid protein, IMT: Immature teratoma, MCT: Mature cystic teratomas, B/L: Bilateral, Rt: Right, Lt: Left

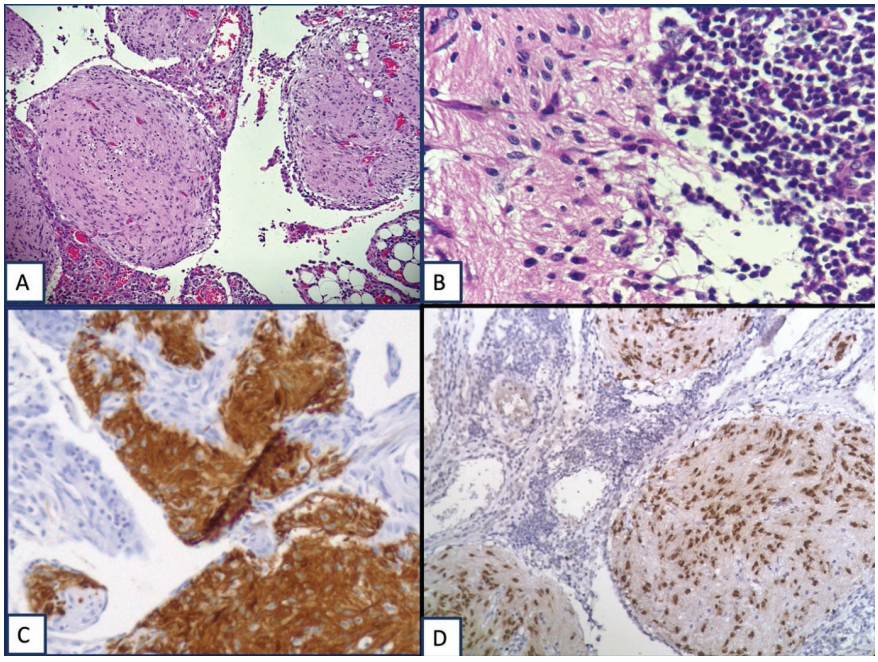

Figure 1. H&E-stained images of foci of GP (A) and nodal GP (B) along with IHC of GFAP (C) and SOX2 on GP foci (D)
H&E: Hematoxylin and eosin, GP: Gliomatosis peritonei, IHC: Immunohistochemical, GFAP: Glial fibrillary acid protein

Table 3. Summary of case series of GP published to date

	Study	Number of cases	Median age (years)	Size (cm)	Ovarian Tm	Diagnosis	Nodal GP	Treatment	Recurrence/ metastasis	Follow-up
1	Wang et al. (1), (2016)	8	20	20.4	IMT: G1: 2, G2-G3: 5, MCT: 1	1st surgery: 6, 2nd surgery: 2	4 (IMT1, MCT 1)	S: 3, S + Ch: 5	No	Alive: 8
2	Liang et al. (4), (2015)	14	NA	NA	IMT: G1: 5, G2-G3: 9	1st surgery: 10, 2nd surgery: 4	3 (IMT1, MCT2)	NA	NA	Alive: 10, NA: 4
3	Bentivegna et al. (5), (2015)	9	36	NA	IMT: G1: 5, G2-G3: 4	1st surgery: 1, 2nd surgery: 8	NA	S: 5, S + Ch: 4	22.2%, (2/9)	Alive: 9
4	Yoon et al. (6), (2012)	16	15	19.8	IMT: G1: 4, G2-G3: 11, MCT:1	1st surgery: 15, 2nd surgery: 1	NA	S: 3, S + Ch: 13	37.5%, (6/16)	Alive: 15, Dead: 1
5	Harms et al. (7), (1989)*	13	11.5	14	IMT: G1:8, G2-G3: 5	1st surgery: 11, 2nd surgery: 2	1 (IMT)	S: 6, S + Ch: 7	No	13
6	Norris et al. (8), (1976)	7	15	25	IMT: G1: 5, G2-G3: 4	1st surgery: 9	NA	S: 4, S + Ch: 1, S + Rx: 2	NA	Alive: 5, Dead: 1, NA: 1
7	Present study	11	29	21.4	IMT: G2-G3: 8, MCT: 3	1st surgery: 11	1 (MCT)	S: 3, S + Ch: 8	No	Alive: 9, NA: 2
	Total	78	NA	NA	IMT G1: 27, G2-G3: 45, MCT: 5	1st surgery: 60, 2nd surgery: 17		S: 24, S + Ch: 37, S + Rx: 2: NA: 14	14.2% (8/56)#	Alive: 68, Dead: 2, NA: 7

*Study was conducted in children and adolescent age group, #Cases with no data on recurrence were not included, GP: Gliomatosis peritonei, IMT: Immature teratoma, MCT: Mature cystic teratomas, S: Surgery, Ch: Chemotherapy, NA: Not available, Rx: Radiotherapy

In these cases 7/10 underwent unilateral salpingo-oophorectomy, along with comprehensive staging surgery. The diagnosis of GP was made after primary surgery in all the cases in our study. Three patients underwent total abdominal hysterectomy (TAH) with bilateral salpingo-oophorectomy (BSO) along with omentectomy, peritoneal lymph node dissection (PLND) and multiple biopsies from various sites. While one of these patients (Case 8) was 34 years of age with a huge adnexal mass of 29 cm, the other (Case 2) was 27 years of age with extensive disease. These patients were diagnosed as IMT on radiology and had multiple deposits spread extensively over the omentum, peritoneum, rectal wall, and bladder wall. Since the exact nature of these deposits was not discernible by radiology alone, a TAH with BSO along with omentectomy and PLND was preferred in these cases. On reviewing all the 10 cases where PLND was performed, all cases were free from metastatic disease and only one had nodal gliomatosis.

As per the NCCN guidelines, patients with IMT having grade 2/3 disease were treated with postsurgical chemotherapy, while those with MCT were treated with surgery alone. The mean follow-up period was 33 months. In terms of outcome, 9/11 patients are alive with no evidence of recurrence or metastasis and two were lost to follow-up.

Discussion

The presence of mature glial tissue implants in the peritoneal cavity is termed GP. It is important to note that these glial implants when benign are graded as grade 0 by the fifth edition of WHO. Since these are found as nodules of varying sizes in the peritoneal cavity they are often misdiagnosed as metastasis or tuberculosis clinically and radiologically (1). The mean age of patients in the present series was 29 years, which was comparable to previous reports in adults, with the exception of Harms et al. (7) who studied the incidence of GP in the child and adolescent age group and found a mean age of 13 years. The mean size of main adnexal mass at 21 cm was also comparable to earlier studies (1).

To date, only 100 cases of GP have been published. A comprehensive literature search identified only six case series that included more than five cases for analysis (1,4-8). Table 3 summarizes the clinicopathological features of GP case studies published to date. Most of these cases have been reported with teratoma of the ovary, though a few cases of mixed germ cell tumors (MGCT) or GTS have also been reported (1,4-9). Of the total of 106 cases of GP, including published case series and various case reports and the present series, we found that only nine cases were associated with MCT and rest were mostly IMT, with five cases of MGCT (1). We did not include cases associated with GTS, as the true nature of these implants is still controversial. The incidence of GP associated with MCT was, however, highest in the present study compared to other studies [36%, 4/11 cases] (4,7,8). One of our cases was a bilateral MCT associated with GP. Yoon et al. (6) reported 15/16 cases of IMT associated with GP, and of these, four were low grade while 11 were high grade. In the present study all IMT were high grade. The largest study of 21 cases, reported by Liang et al. (4), reported 14 cases of IMT, six cases of MGCT and only one case of MCT associated with GP. There were no cases of MGCT with GP in our archives.

Though the exact etiology of GP is still unknown, two main hypotheses related to its origin have been proposed (8,10). The first largely relates to the presence of capsular breach in the primary teratoma, leading to the development of mature glial implants. This hypothesis also includes the possibility of lymphovascular spread of mature glial tissue, as is evident from nodal gliomatosis found in the literature. We found capsular breach in 7/10 of our cases, including six IMT and one MCT. Robboy and Scully (11) reported similar findings in 11 of 12 cases in their report. Kim et al. (12) reviewed 100 cases of

Table 4. Summary of cases showing LN gliomatosis in the literature and the present study

Author and year	Journal	Age	LN sites	Primary tumor	Treatment	Prognosis
Liang et al. (4), (2015)	Mod. pathology	18	LN	IMT - G1	NA	Alive at 19 months
		42	LN	MGCT	NA	Alive at 23 months
		20	LN	MGCT	NA	Alive at 11 months
Wang et al. (1), (2016)	Journal of Ovarian Research	25	Iliac	MCT	S	Alive 3 months
		16	Iliac	IMT G2	S + Ch	Alive 68 months
		22	Iliac	IMT G1	S + Ch	Alive 60 months
		17	Iliac	IMT G3	S + Ch	Alive 144 months
Kim et al. (12) (2013)	Korean Journal of Pathology	34	Hypogastric	IMT G1	S	Alive at 9 months

Table 4. Continued

Author and year	Journal	Age	LN sites	Primary tumor	Treatment	Prognosis
Fang et al. (13), (2015)	Zhonghua Bing Li Xue Za Zh	20	Paraaortic	IMT G3	S + Ch	Alive at 36 months
Chou et al. (14), (2005)	Taiwanese J of Obstet Gynecol	36	Omental	MCT	S	Alive at 12 months
Khan et al. (15), (2005)	Gynecol Oncol	23	LN	IMT G1	S + Ch	NA
Perrone et al. (16), (1986)	Arch Pathol Lab Med	10 months	Paraaortic	IMT G1	S	Alive at 9 months
El Shafie et al. (17), (1984)	J Surg Oncol	12 years	Omental	MCT	S	Alive at 5 years
Nagashima et al. (18), (1974)	Acta Pathol Jpn	22	Inguinal, mesenteric, mediastinal, cervical	IMT	S + Ch	Dead at 8 months
Benirschke et al. (19), 1960	Obstet Gynecol	18	Retroperitoneal, iliac, cervical axillary	MCT	Ch + radiotherapy	Dead at 8 months
Alna'irat et al. (20), (2023)	Int J Gynecol Pathol	23	Pelvic LN	IMT	S + Ch	Alive
Present study (2023)		27	Pelvic and omental	MCT	S	Alive at 48 months

LN: Lymph node, IMT: Immature teratoma, MCT: Mature cystic teratomas, MGCT: Mixed germ cell tumors, S: Surgery, Ch: Chemotherapy, NA: Not available, Mod. pathology: Modern pathology

GP and found nine cases with nodal gliomatosis in pelvic or para-aortic LN. Three of these cases were, however, not true nodal GP, as they had teratomatous components along with glial implants. In 2016, Wang et al. (1) reported eight cases with GP, of which three had nodal GP. Recently, Alna'irat et al. (20) reported a case of nodal GP with ITM in a young girl and reviewed the literature on nodal GP. In their review they also explained nodal GP on the basis of metaplasia of nodal mesothelial cells, secondary to factors secreted by the primary ovarian neoplasm. Table 4 summarizes the cases showing nodal gliomatosis from the reviewed literature. There were 17 cases of nodal gliomatosis, of which five were associated with MCT (including the case presented here), 10 with IMT and two were MGCT (1,4,12-20). Moreover, the occurrence of GP following ventricular-pontine shunts, as reported by Lobotesis et al. (21), also favoured this theory.

In the search for the pathogenesis of GP, Ferguson et al. (22), in 2001, used polymorphic microsatellite (MS) in two cases of GP and found that, like normal tissue, GP foci were also heterozygous while the teratoma cells were homozygous for MS loci (19). This supports the second hypothesis concerning the origin of GP, which suggests that glial foci are genetically not associated with teratoma and instead arise from metaplasia of normal cells, such as peritoneal cells or pluripotent Mullerian stem cells (22). Cases reported by Bässler et al. (23), Killeen et al. (24) and the study conducted by Kim et al. (12) where GP was found to coexist with endometriosis, further supports this metaplasia hypothesis (25). The authors also believed that the teratomas may secrete some factors that stimulates glial differentiation affecting not only peritoneal stem cells but also leading to glial differentiation in the tumor itself. In all our cases of teratoma associated with GP, we found an average of 20% mature glial differentiation (range; 5-45%) in the main tumour. Liang et al. (4) performed IHC for SOX2, OCT4 and NANOG in nine cases of GP. In accordance with their observation, all our cases were also positive for SOX2 and immunonegative for OCT4, indicating that SOX2 may have an important role in the development of GP. The observation of Nogales et al. (26) that SOX2 plays a major role in maintaining pluripotency of stem cell and that of Maucksch et al. (27) establishing the key role of SOX2 in inducing stem cells towards neural differentiation, further supports the metaplastic hypothesis. Moreover, SOX2 is also expressed in neural stem cells, IMTs, endodermal derivatives of mature teratomas and glial tumors, suggesting that SOX2 may lead to the development of GP in association with other transcription factors (28). Figure 2 summarizes the various hypotheses pertaining to the pathogenesis of GP. However, since GP is such a rare condition, the exact mechanism leading to the development of glial follicles in the peritoneum still needs to be discerned.

The first is that it may arise from cancer stem cells within IMTs or from IMTs that may have undergone maturation. The second hypothesis supports the development of GP from peritoneal stem cells that differentiate towards a neural lineage, as induced by various factors secreted by teratomas. The third hypothesis suggests that GP may actually derive from subperitoneal

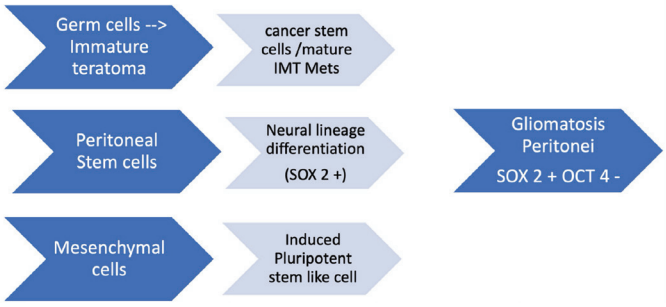

Figure 2. Summary of hypotheses concerning the pathogenesis of gliomatosis peritonei

mesenchymal stem cells that either directly transdifferentiate into glial cells or are converted to an induced pluripotent stem, as in cell forming mature glial nodules.

While MCT are managed by surgery alone (cystectomy/salpingo-oophorectomy), IMT stage 1 and grade 1 are managed by surgery (fertility sparing surgery with comprehensive staging, if desirable of fertility or a completion staging surgery if fertility is not desired) followed by observation, as per published Guidelines. High grade IMT (grade 2 or 3) or stage 2 and above diseases, on the other hand, are treated with surgery and a chemotherapy regimen. All cases in our study were high grade IMT (7/10), and thus were treated with surgery followed by chemotherapy. In the literature review, out of a total of 77 cases of OT with GP, 24 patients were treated with surgery and 37 patients were treated with both surgery and chemotherapy. Prognosis in these cases depended predominantly on the stage and grade of the primary tumor and on the grade of its metastatic tumor deposits.

In 1970, when Robboy and Scully (11) reviewed 12 cases of OT with glial implants, they concluded that the prognosis of OT or metastasized OT was favorable when associated with mature glial tissue implants. However, later in 2002, Müller et al. (25) reported 11 cases of GP with adverse outcomes. It was reported that in all these cases, adverse outcome was attributable to lack of histological sampling at the time of first surgery. It is thus advisable to take multiple biopsies and perform adequate sampling at the time of first surgery to rule out immature glial/teratoma implants as the treatment regime, as well as prognosis, depends on their presence. Nonetheless, ovarian IMT with GP has a better prognosis when compared with respective grades of primary IMT. In our review of 77 cases, though 45/77 cases were high grade IMT, 68/70 patients for whom data was available were alive. In 14.2% of our review cases, recurrence was reported. None of our 11 cases have reported recurrence so far.

Since GP is difficult to remove completely, residual disease is left post surgery in most of the cases. On rare occasions milliary spread of IMT has been reported. Post-surgery, chemotherapy induces a change in immature elements to mature elements. This is known as chemotherapeutic retroconversion or GTS (29). GP may sometimes be confused with GTS, especially when GP is diagnosed on second surgery. However, unlike GTS, it is not essential for GP to have a prior history of chemotherapy. Moreover, the implants associated with GP are composed exclusively of mature glial tissue, while GTS may have other mature teratoma components as well. This distinction between GP and GTS is critical to decide the further course of treatment. It is imperative in GTS cases to do an optimal cytoreductive surgery to avoid future complications, like bowel obstruction. Conversely, as GP cases are usually asymptomatic and known to be quiescent for long periods, they are managed by observation and follow up after the treatment of the primary associated OT (6). It is also believed that since nodal GP has a better prognosis, adjuvant chemotherapy is not recommended in such cases. Over a period, these GP foci either undergo fibroblastic transformation and gradually disappear or sometimes are detected at the time of second surgery (25,30). There is also a very rare chance for malignant transformation in GP. Shefren et al. (31) reported a 16-year girl with IMT with GP who developed a malignant glial neoplasm five years after the original surgery. Moreover, since GP with IMT cases are also associated with more frequent recurrences, a close, long-term follow-up is advised, given the rare but present chance for malignant transformation (31).

Study limitations

Although the incidence of GP is rare, 11 cases of GP are presented, along with IHC markers that suggest a stem cell origin of GP. Since only 11 cases were included, the absence of molecular confirmation following IHC immunopositivity of GP cells, confirming a stem cell origin, constituted the main limitation. More studies should be planned in future to establish a clear pathogenesis in these cases.

Conclusion

Though mostly associated with IMT, the incidence of MCT with GP was not infrequent. A possibility of GP must also be considered as a differential, clinically and radiologically, in cases of omental nodularity. Adequate sampling at the time of surgery is essential to rule out metastasis or GTS. The identification of mature glial tissue in primary ovarian neoplasm (with or without capsular breach/metastasis) associated with GP and nodal gliomatosis only favors the metaplastic theory of the origin of GP. SOX2, a stem cell marker inducing neural differentiation, may play a crucial role in the development of GP in association with other transcription factors. Since the prognosis is favourable and residual disease is dormant, a

conservative approach should be preferred, along with long-term follow-up to detect malignant transformation, if any. Further research must be taken to understand the factors contributing to the occurrence of GP and also for nodal gliomatosis.

Ethics Committee Approval: *Since this study was performed on retained histopathological samples from the departmental archives, ethics approval was not taken as per our institutional review board guidelines.*

Informed Consent: *Retrospective study.*

Author Contributions: *Surgical and Medical Practices: J.B.S.; Concept: R.R., S.K., J.B.S., S.R.M.; Design: R.R., S.K., J.B.S., S.R.M.; Data Collection or Processing: R.R., S.K., J.B.S.; Analysis or Interpretation: R.R., S.K., J.B.S., S.R.M.; Literature Search: R.R., S.K., J.B.S., S.R.M.; Writing: R.R., S.K., J.B.S., S.R.M.*

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Prevalence of premenstrual syndrome and related factors among nurses

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Abstract

Objective: Premenstrual syndrome (PMS) is a common condition among women during their menstrual cycle. PMS can negatively affect a woman's daily life and function. Nurses, as an important and substantial segment of healthcare staff, are affected by the demanding environment of work place. Since PMS, as a prevalent counterproductive condition, has not been studied in this population in Iran, we assessed the prevalence of PMS and its associated factors among nurses aged 23 to 49 in teaching hospitals of the Tehran province of Iran.

Material and Methods: In this cross-sectional study from April 2021 to January 2022, 280 participants from teaching hospitals were enrolled. Simple random sampling was used to determine the sample size of the study. Two validated questionnaires and a data gathering sheet were used to collect information. The premenstrual symptoms screening tool was used to determine PMS severity and the Copenhagen Psychosocial Questionnaire to evaluate the associated job demands. Demographic data and work-related data included: night shift, shift type, monthly COVID-19 care and gynecologic and past medical history were gathered. Then data were analyzed using logistic regression analysis, chi-square and t-test.

Results: The severity of PMS was: mild (42.5%); moderate (30%); and severe (27.5%). Regular menstruation and dysmenorrhea were reported by 84.6% and 72.3%, respectively. Moderate to severe PMS was associated with: monthly COVID shift ($p=0.02$); emotional ($p<0.01$) and quantitative ($p<0.01$) demands; regular caffeine intake ($p=0.01$); education level ($p=0.005$); regular exercise ($p=0.003$); regular fiber intake ($p=0.08$); and irregular menstrual cycles ($p=0.007$). In logistic regression only quantitative ($p=0.003$) and emotional ($p=0.018$) job demands were significant.

Conclusion: Results showed that the prevalence of PMS was high among Iranian nurses and was associated with quantitative and emotional job demands. We suggest further studies focusing on preventative and effective interventions to diminish the consequences of PMS in this population. We also suggest investigating the practical application of the findings of this study for healthcare professionals and policymakers. (J Turk Ger Gynecol Assoc 2024; 25: 74-80)

Keywords: Premenstrual syndrome, nurses, job demands, occupational stressor

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Introduction

Premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) are common conditions that are characterized by associated physical and psychological symptoms, which occur during the luteal phase of an individual's menstrual cycle, and have a significant impact on a woman's functionality (1). PMDD and PMS resolve after menstruation without any necessary intervention (2). The physical symptoms usually include a variety of pains, such as headaches, abdominal pains, mastalgia, and back pain, and nausea or constipation are also reported to be prevalent (3). The psychological symptoms, which may severely interfere with routine daily functioning, include anxiety, mood changes, anger, depression, agitation, restlessness, and sleep problems or insomnia (4). Although various risk factors and etiologies have been suggested for

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PMS/PMDD, the precise pathophysiology of these syndromes is not completely understood. Genetic susceptibility has also been suggested as a possible explanation for these disorders and some studies have found a significant association between the *estrogen receptor alpha 1 (ESR1)* gene and PMS (5-7). Other risk factors include obesity, smoking, and pre-existing anxiety disorder (8).

The prevalence of PMS has been estimated to be more than 50% among menstruating women (1). A systematic review and meta-analysis reported the prevalence of PMS to be 47.8% with an increasing trend from 1996 to 2011. The lowest prevalence was in France (12%) and the highest was in Iran (98%) (9). In a more recent study it has also been reported that the worldwide prevalence of PMS is 47.8% (10) of which 20% suffer from such severe symptoms that they interfere with daily routines while the remainder experienced mild to moderate symptoms (11). However, based on a recent systematic review and meta-analysis in Iran, the prevalence of PMS varied from 30% to 99% (12). Further epidemiological studies should investigate the global and national prevalence of this syndrome.

PMS as a major health problem impacts the ability of affected nurses to perform their normal roles and may compromise the outcome and safety of patient care (13). Women form a large proportion of healthcare staff in Iran and most work as nurses. Thus, PMS may have a major impact on the functioning of the Iranian healthcare system.

Studies in Korea have shown that PMS prevalence was 36.1% in adolescents and 38.1% in women of childbearing age (14), while its prevalence was 98.1% to 100% in female college students (15). In a study by Tsai et al. (16) on a population of female employee in Taiwan, the prevalence of the symptoms of PMS was reported to be 24% for fatigue, 21.2% for headache and 17.4% for abdominal bloating. In some studies it has been reported that PMS is mostly affecting female university students (11) and this observation is supported reported prevalence rates in Turkey of 72.1% to 91.8% (17), Japan at 79% (18), and Egypt at 65% (19).

Nurses have a critical role in healthcare provision in any healthcare system. Certain conditions, such as a high workload or stressful working environment and their crucial responsibilities may negatively affect their general health and job satisfaction (20). As there are few studies investigating the prevalence of PMS and its associated factors among nurses, the present study aimed to investigate the prevalence of PMS among nurses and its associated factors in Iran.

Material and Methods

The research questions for the present study were:

- How are quantitative and emotional demands associated with the severity of PMS among nurses?
- Are lifestyle factors, such as regular exercise, caffeine intake, and fiber intake related to the occurrence and severity of PMS in nurses?
- Is there a relationship between monthly shifts and the prevalence and severity of PMS?
- Are background disease history and regular menstruation related to PMS?

In this cross-sectional study, participants from teaching hospitals in Tehran province of Iran were included and the study period was from April 2021 to January 2022. Simple random sampling was used and to determine the sample size, the formula of was used. Our sample is the known universe. The inclusion criteria were: being a serving nurse and being aged between 23 and 49 years. Participants who were older than 49 years old, were pregnant, used hormonal drugs or had any underlying psychological disorder were excluded from this study.

Two validated questionnaires were used to gather data. We also used a data-gathering sheet for information regarding demographic characteristics (age, marital status, socioeconomic status, physical activity, daily habits such as smoking, coffee intake frequency, and other dietary habits). Past medical history included any psychological disorders and all chronic diseases. Work related data included: day or night shift, shift type, monthly COVID-19 shift. Gynecologic data included: menarche age, regular menstruation cycle, dysmenorrhea, menstruation duration and using contraception.

The first validated questionnaire used was the premenstrual symptoms screening tool (PSST) questionnaire, developed by Steiner et al. (21). This was validated in Persian by Hariri et al. (22) with a Cronbach's alpha coefficient of 0.93, content validity by Content Validity Ratio and Content Validity Index of 0.7 and 0.8, respectively, showing it was suitable for use in an Iranian female population. The PSST evaluates premenstrual clinical symptoms and their severity a week before menstruation and disappearance after it. PSST comprises two separate domains. The first domain has 14 items regarding the psychological, physical, and behavioral aspects of PMS while the second domain with five items, focuses on functionality and social and family connections of the subjects. The items are rated on a four-point scale (not at all: 0, mild: 1, moderate: 2, severe: 3).

The job demand domain from the medium version of the Copenhagen Psychosocial Questionnaire (COPSOQ) was used to determine occupational stressors (23,24). The Persian version COPSOQ was previously validated by Arsalani et al. (25) with a Cronbach's alpha and intraclass correlation coefficient of 0.60 and 0.70 respectively, and also proved to be applicable for work situation studies such as studies on nurses. This job demand domain has five scales include: quantitative (4 questions), emotional (3 questions), demand

to conceal emotion (2 questions), cognitive (4 questions), and sensorial demands (4 questions). The score of the domain is calculated by adding the scores of scales. A higher score indicates more unfavorable psychosocial conditions in the work place.

Ethical Consideration

All ethical considerations have been addressed to respect the rights and dignity of the studied population. Participants joined the research voluntarily and signed an informed consent prior to data gathering and were free to leave the study. Anonymity and confidentiality were ensured. The Ethics Committee of Tehran University of Medical Sciences approved this study (approval number: IR.TUMS.MEDICINE.REC.1399.681, date: 28.10.2020).

Statistical analysis

Data was analyzed using IBM SPSS for Windows, version 24.0 (IBM Corp., Armonk, NY, USA). Due to the high prevalence of PMS among the participants in this study, we divided the participants into two groups; a) those with mild and b) those with moderate to severe symptoms. The categorical and numerical variables were reported using descriptive statistics. The association of different variables was evaluated using t-test and chi-square test. A p-value less than 0.05 was considered statistically significant. All the variables were normally distributed.

For comparison between a qualitative variable (PMS) and quantitative variables, we have used an Independent sample t-test was performed initially, followed by regression analysis. Similarly, for comparison of the relationship between PMS severity and qualitative variables, a chi-square analysis was performed.

For the final assessment of variables showing significance by Independent samples t-test, logistic regression was performed.

Results

Demographic characteristics and COPSOQ score

A total of 323 individuals were eligible for the study but after exclusions, the study population numbered 280. The mean ± standard deviation age and body mass index (BMI) of 280 participants were 33.42±7.42 years and 24.6±3.51 kg/m^2, among which 42.5%, 30%, and 27.5% suffered from mild, moderate, or severe PMS, respectively. Having a regular caffeine intake (p=0.01), having a Master's degree rather than a Batchelor degree (p=0.005), and poor dietary fiber consumption (p=0.048) were associated with PMS severity, but other demographic variables listed in Table 1, 2 did not show association with PMS prevalence and PMS severity. Emotional and quantitative demands from job demands variables (COPSOQ questionnaire) were associated with PMS and PMS severity (p=0.001) (Table 1).

Health- and work-related characteristics

Irregular menstruation cycle was associated with higher rates of moderate to severe PMS (p=0.007). Nurses that didn't exercise regularly reported more severe PMS (p=0.003). Monthly COVID shift was associated with PMS severity, such that moderate to severe PMS cases had more shift months dealing with patients suffering from COVID-19 (p=0.02). Other health- and work-related characteristics of participants are summarized in Table 2 and showed no significant difference regarding PMS severity (Table 2).

Job demands

Based on logistic regression analysis (Table 3) quantitative/workload demand and emotional demand were significantly associated with PMS severity. Severe PMS was associated with higher workload [p=0.003, odds ratio (OR): 1.06], and emotional demands (p=0.018, OR: 1.04), but sensorial demands and cognitive demands did not show any association with PMS severity.

Discussion

PMS has a complex pathophysiology that has not yet been fully understood. PMS is believed to be caused by the action of progesterone on some neurotransmitters, such as catecholamine, serotonin, opioids and gamma-aminobutyric acid. Another situation that may lead to PMS is when serotonin is less than the optimal level and then the sensitivity to progesterone is increased. Other conditions that are believed to have roles in PMS occurrence are increased prolactin level, increased sensitivity to the effect of prolactin, alterations in the metabolism of glucose, abnormal function of the hypothalamic-pituitary-adrenal axis, insulin resistance, some nutritional and electrolyte deficiencies and genetic tendencies. In addition, stress can trigger the activity of the sympathetic nervous system which results in intense uterine contractions, causing menstrual pain (11).

The results of the present study showed that more than 42.5% of nurses in the teaching hospitals included in the study suffered from mild PMS and 57.5% suffered from moderate or severe PMS. In logistic regression analysis, PMS severity was significantly associated with irregular menses, higher education level, having to undertake COVID-19 shifts, higher workload and emotional job demands. In a study on female knitting workers, it was reported that stress menstrual disorders may be a result of high stress levels, resulting in disturbed hormone homeostasis with low testosterone levels, and high follicle stimulating hormone and estradiol 2 levels (26).

Table 1. Comparing the relationship between PMS severity and different quantitative variables and mean values obtained from assessment of psychosocial job demand domain and its scales of Copenhagen questionnaire and PMS severity

Variable	Mild (mean ± SD)	Moderate to severe (mean ± SD)	p-value
COVID shift/months	**16.44±8.84**	**20.25±10.97**	0.02
Income	7.27±2.21	6.96±1.89	0.23
Age	32.88±7.46	33.84±7.38	0.28
BMI	24.38±3.36	24.91±3.61	0.21
Age of menarche	13.53±1.78	13.31±1.59	0.31
Menstrual duration	6.39±1.42	6.21±1.41	0.33
Emotional demands	47.86±18.24	62.01±19.09	<0.01
Cognitive demand	63.04±19.15	66.25±18.18	0.16
Quantitative demand	49.13±20.00	65.14±18.68	<0.01
Sensorial demands	79.96±17.68	80.43±16.90	0.82
PMS: Premenstrual syndrome, SD: Standard deviation, BMI: Body mass index, COVID: Coronavirus			

Table 2. Comparing the relationship between PMS severity and different qualitative variables

Variables	Class	Mild, n (%)	Moderate to severe, n (%)	p-value OR (CI, 95%)
Marital status	Single	51 (43.2)	67 (56.8)	0.83 1.05 (0.65-1.70)
	Married	68 (42.00)	94 (58.00)	
Regular caffeine intake	No	78 (49.40)	80 (50.60)	0.01 1.90 (1.16-3.10)
	Yes	42 (33.90)	80 (66.10)	
Education	Bachelor	119 (45.40)	138 (54.60)	0.005 4.36 (1.45-13.07)
	Master	2 (16.0)	21 (84.0)	
Regular exercise	No	84 (38.00)	137 (62.00)	0.003 0.42 (0.23-0.75)
	Yes	35 (59.30)	24 (40.70)	
Dietary fiber intake	No	12 (28.60)	30 (71.40)	0.048 0.49 (0.23-1.00)
	Yes	107 (45.00)	131 (55.00)	
Meat consumption	No	17 (35.60)	29 (64.4)	0.29 0.70 (0.36-1.36)
	Yes	103 (44.00)	131 (56.00)	
Regular menstruation	Yes	108 (46.1)	127 (53.90)	0.007 0.36 (0.17-0.77)
	No	11 (23.80)	34 (76.20)	
Dysmenorrhea	Yes	82 (40.20)	121 (58.80)	0.20 1.41 (0.82-2.40)
	No	38 (48.70)	39 (51.30)	
Prevention	Yes	37 (44.00)	47 (56.00)	0.76 0.92 (0.54-1.55)
	No	74 (42.00)	102 (58.00)	
Disease hx.	Yes	11 (28.20)	29 (71.80)	0.050 2.07 (0.98-4.37)
	No	108 (45.00)	132 (55.00)	
Shift type	Fixed (%)	34 (38.90)	51 (61.10)	0.68 0.89 (0.51-1.55)
PMS: Premenstrual syndrome, OR: Odds ratio, CI: Confidence interval, Disease hx.: Positive disease history				

Table 3. Multiple logistic regression modeling (other variables were also included in this model)

Variable	B	p-value	OR	95% CI for OR	
				Lower	Upper
Emotional demand	0.046	0.018	1.04	1.008	1.08
Workload demand	0.065	0.003	1.06	1.58	18.52
Monthly COVID shift	0.05	0.06	1.05	0.99	1.11
Regular menstruation	-1.62	0.06	0.19	0.03	1.1
Disease history	1.6	0.07	4.96	0.87	28
R^2: 42%, OR: Odds ratio, CI: Confidence interval, COVID: Coronavirus					

In contrast, variables such as income, age, BMI, age of menarche, menstrual duration, cognitive demand, and sensorial demands did not show significant differences between the two PMS severity groups in the present study.

According to a study of nursing students in Turkey, the prevalence of PMS was about 36% among the 250 students enrolled in the study compared to 100% prevalence of PMS in our study (27). This remarkable difference has been observed in other studies as well. A meta-analysis conducted on the prevalence of PMS, showed that Iran has the highest prevalence of PMS, globally, with a prevalence of 98% (7). However, in the aforementioned meta-analysis, only one study from Iran was included in the meta-analysis and thus, this number could be an overestimation of the prevalence of PMS in Iran. Based on several studies on different populations of women, the prevalence of PMS among Iranian population is estimated to be approximately 50 to 80% (28,29). The prevalence is particularly high in healthcare providers and is strongly associated with quality of life and social relationships in Iran (30). A study of work-related quality of life in nurses in Turkey found that PMS was associated with reduced quality of life (13). The result of our study is in concordance with previous studies in this regard. A review of the literature showed that precise estimation of the prevalence of PMS and PMDD at the national level in Iran is not available. Considering the importance of this syndrome and its impact on daily activities, quality of life, and social life, it is recommended that future studies should determine the prevalence of this PMS/PMDD by conducting nation-wide surveys.

The present study showed that there was a significant relationship between regular physical activity and the severity of PMS. Similar results have been reported in other studies. According to the latest systematic review and meta-analysis of the effects of physical activity on PMS in 2020, exercise has been shown to improve physical symptoms, such as pain, constipation, breast tenderness, and psychological symptoms such as anxiety and anger. Although exercise does not affect other symptoms and has more of a soothing role, it can be concluded that exercise can be recommended as a possible intervention to reduce the severity of PMS symptoms. However, there is no guidance regarding the duration and intervals between episodes of physical activity and its effect on PMS (3).

Our study found no significant association between marital status and PMS severity. However in another study on the relation between the lifestyle of Jordanian females and PMS, marital status was found to have association with PMS in a way that psychological symptoms were higher with marital status while behavioral symptoms were lower with it (31).

Furthermore, education level demonstrated a significant association with PMS severity, suggesting a strong association between higher education and moderate to severe PMS. This finding was in line with another study on female workers in a psychiatric hospital in which higher education level was associated with more PMS symptoms (32).

In addition, dietary fiber intake was found to be significantly associated with PMS severity, showing a potential protective effect against moderate to severe PMS. In another study the duration of PMS symptoms was reported to be reduced by low fat and high-fiber diets (33).

Other variables such as meat consumption, dysmenorrhea, prevention, and shift type did not show significant associations with PMS severity.

In the present study, no association was found between PMS and either age or BMI. A similar study on the prevalence of PMS among operating room technicians found similar results (34). Of the 112 technicians in the study, 57% had severe or moderate PMS and 43% had mild symptoms. No significant association was found between ages or BMI. According to the results of this study, the prevalence of PMS was lower among technicians with regular physical activity and less stress. In the present study there was a significant association between PMS severity and caffeine consumption, so that taking caffeine regularly increased severity of PMS. A similar study was performed on a population of nurses in Thailand, in which the prevalence of PMS was higher in the nurses who consumed more than one cup containing caffeine a day. However, among these variables, only caffeine consumption was significantly associated with PMS (35). Other studies have not reported

an association between caffeine consumption and PMS (36). Further research is needed to determine the relationship between caffeine consumption and its possible effect on the prevalence and severity of PMS.

The results of the present study showed that there was a significant association between irregular menstruation and PMS severity. Our results are in line with a similar study from Japan, in which logistic regression analysis revealed that stress scores, heavy menstrual bleeding, and dysmenorrhea were significant predictors of PMS symptoms (37). The results showed that psychosocial stress was independently related to PMS and the experience of irregular menstrual cycles. These authors suggested that stress was the most important factor in increasing the risk of PMS, dysmenorrhea, and irregular menstrual cycle.

Severity of PMS was significantly associated with emotional and workload needs in our study. Sex hormones, such as estrogen, progesterone and testosterone have significant effects on the brain, behavior and cognitive function. However, it is still unclear whether any identified cognitive impairments are attributed to the negative experiences of mood and psychological symptoms or are a direct consequence of hormonal dysregulation. There is a dearth of published evidence regarding cognitive function during the menstrual cycle (38). However, the existing literature using robust methodologies does not appear to show significant effects of the menstrual cycle on cognitive function. Besides, menstrual cycle fluctuations may be too transient to reveal significant findings (38).

The monthly COVID shift was associated with PMS severity, such that nurses reporting moderate to severe PMS had more shift months. This finding is in line with the results from other studies in which PMS was associated with shift working due to sleep quality and sleep time variability (39), which could result from a disrupted circadian rhythm (40).

In the present study, disease history encompassing every chronic disease, was shown to have the potential to impact PMS. Previous research has also demonstrated that underlying diseases, such as diabetes mellitus, hypertension, renal disease, anxiety, and depression were risk factors for PMS (41).

Lastly, our study included all nurses aged 23 to 49 years from the teaching hospitals of Tehran University of Medical Sciences, providing a practical sample of Iranian healthcare workers. A host of demographic, work-related, and quality of life variables was assessed and compared regarding PMS severity. Furthermore, detailed quality of life, occupational, and performance-related factors were investigated in nurses with regard to PMS severity. Nonetheless, the causality of these variables cannot be determined through the current study; establishing a causal association among these many variables would require longitudinal studies recruiting large samples. Further interventional studies may aid in identifying counter-measures to alleviate difficulties associated with PMS.

Study limitations

In terms of the limitations of the present study, since this was a cross-sectional study that was conducted in one section, the generalizability and causality are limited. Also, some of the data are self-reported which makes the recall bias probable.

Conclusion

PMS is common among nurses in Iran and its prevalence is remarkably high in comparison with other countries. PMS was associated with reduced quality of life, and focus disturbances. Several variables were shown to be associated with worse symptoms of PMS but only work place workload and emotional demand were shown to be associated using regression analysis. Therefore, further studies should focus on prevention strategies in order to reduce its prevalence or offer effective interventions to reduce its complications in the work place.

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Informed Consent: *Participants joined the research voluntarily and signed an informed consent prior to data gathering and were free to leave the study.*

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Comparison of perinatal and neonatal outcomes of symptomatic pregnancy infected with SARS-CoV-2

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Abstract

Objective: In this study, maternal and neonatal outcomes of pregnant women with positive severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) RNA tests were evaluated according to their symptomatic status. The clinical progression of SARS-CoV-2-positive pregnant women and the effect of coronavirus disease-2019 (COVID-19) on newborns was investigated.

Material and Methods: This retrospective cohort study was conducted at a tertiary pandemic hospital specializing in caring for pregnant women infected with SARS-CoV-2. We included patients with a positive SARS-CoV-2 polymerase chain reaction test at delivery, subdividing them into symptomatic and asymptomatic groups.

Results: Two hundred and forty-nine patients were included in the study. The mean age of the pregnant women in the symptomatic group was higher than those in the asymptomatic group ($p=0.001$). The iatrogenic preterm birth rates in the symptomatic and asymptomatic groups were 43.37% and 8.43%, respectively ($p<0.001$). Cesarean section rate was higher in symptomatic group ($p=0.01$). Maternal death was significantly higher in symptomatic pregnant women ($p<0.001$). The neonatal intensive care unit admission rate was higher in symptomatic pregnant women ($p<0.001$).

Conclusion: The maternal and fetal outcomes for mothers with symptomatic infections tend to be worse, highlighting the importance of careful management, good follow-up and the advisability of closer monitoring. (J Turk Ger Gynecol Assoc 2024; 25: 81-9)

Keywords: COVID-19, maternal outcomes, pregnancy, preterm birth

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Introduction

In December 2019, pneumonia cases of unknown origin were reported in the city of Wuhan, China (1). The virus isolated from respiratory tract samples taken from these cases was named severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) (2). The virus resulted in the coronavirus disease-2019 (COVID-19) global pandemic (3). Due to the physiological adaptation mechanisms induced by pregnancy, it was predicted that COVID-19 may progress more severely in pregnant women. Many researchers have attempted to define the clinical course of COVID-19 in pregnant women, how the disease affects pregnancy and delivery results, which factors affect the severity of the disease and how much it worsens these results (4). In this study, maternal and neonatal outcomes of pregnant women with positive SARS-CoV-2 RNA tests at delivery were evaluated according to their symptomatic status. Anticipating the complications that may occur in the management of symptomatic COVID-19-positive pregnant women, it was planned to implement necessary medical interventions earlier in the study population. Whether there was a difference between the postpartum clinical course of symptomatic COVID-19-infected pregnant women and the clinical course of their newborns and asymptomatic COVID-19 pregnant women was investigated.

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Material and Methods

This retrospective cohort study was conducted at a tertiary pandemic hospital specializing in caring for pregnant women infected with SARS-CoV-2. The data of patients who were confirmed to have COVID-19 by reverse transcription polymerase chain reaction (PCR) test from the nasopharyngeal swab and who gave birth between March 1, 2020, and December 31, 2022, were analysed retrospectively from electronic health records. The collected data were anonymized. The procedures followed were approved by the ethical standards of the responsible committee on human experimentation and in keeping with the Helsinki Declaration of 1975, revised in 2013. COVID-19-positive patients with other reasons for elevated serum liver transaminases, C-reactive protein (CRP), leukocytes, and chronic illness were excluded from the study. Lung ultrasonography (LUS) before delivery and thorax computed tomography (CT) after delivery were performed in all pregnant women. Patients with a positive SARS-CoV-2 PCR test at delivery were included, subdivided into symptomatic and asymptomatic groups. Demographic characteristics, obstetric outcomes, newborn outcomes, maternal laboratory results, maternal intensive care unit (ICU) admission, maternal mortality, and clinical features were compared between the two groups. The University of Health Sciences Turkey, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Institutional Ethics Committee approval was granted (approval number: 165, date: 14.12.2022).

Statistical analysis

Data were statistically analysed using the SPSS, v.21.0 (IBM Inc., Armonk, NY, USA). The Shapiro-Wilk test was used to check whether data were normally distributed. Continuous variables are expressed as mean and standard deviation or median and range, as appropriate. Categorical variables were expressed as frequency and percentage. The Independent t-test was used to compare continuous variables, as appropriate. The Pearson's chi-squared test or Fisher's exact test were used to compare qualitative data. A logistic regression analysis was performed. A p-value <0.05 was considered statistically significant.

Results

The study included 249 pregnant women, of whom 166 (66.66%) were asymptomatic and 83 (33.34%) were symptomatic. Of the symptomatic patients, 57 (68.7%) had shortness of breath, 22 (26.5%) had cough, and 4 (4.8%) had fever.

The mean ages of the pregnant women in the symptomatic group were higher than those in the asymptomatic group (p=0.001) (Table 1). The nationalities of the pregnant women were evaluated and 155 (93.37%) in the asymptomatic group

Table 1. Comparison of maternal demographics with symptomatic status

	Asymptomatic (n=166)	Symptomatic (n=83)	p
Maternal age (years)	28.91±5.50	31.10±4.73	**0.001**
Nationality			0.333
Turkish	155 (93.37)	80 (96.38)	
Arabic	11 (6.63)	3 (3.62)	
COVID-19-year			
2020	39 (23.5)	15 (18.1)	0.328
2021	98 (59)	62 (74.7)	**0.015**
2022	29 (17.5)	6 (7.2)	**0.028**
BMI (kg/m^2)	26.65±3.62	27.50±3.72	0.085
Blood type			0.403
A	74 (44.57)	39 (46.98)	
B	22 (13.25)	9 (10.84)	
AB	13 (7.83)	10 (12.04)	
0	57 (34.33)	25 (30.12)	
Rhesus			0.894
Positive	145 (87.34)	72 (86.74)	
Negative	21 (12.65)	11 (13.25)	
Gravida	2 (1-8)	2 (1-7)	0.091
Parity	1 (0-6)	1 (0-6)	0.133
Abortion history	0 (0-4)	0 (0-3)	0.196

Table 1. Continued

	Asymptomatic (n=166)	Symptomatic (n=83)	p
Chronic disease	26 (15.6)	14 (16.8)	0.880
Hypothyroidism	13 (7.8)	7 (8.4)	
Hyperthyroidism	1 (0.6)	0 (0)	
Diabetes mellitus	3 (1.8)	2 (2.4)	
Asthma	5 (3.0)	3 (3.6)	
Cardiac arrhythmia	1 (0.6)	0 (0)	
Celiac disease	1 (0.6)	1 (1.2)	
Epilepsy	1 (0.6)	0 (0)	
FMF disease	0 (0)	1 (1.2)	
Behçet's disease	1 (0.6)	0 (0)	

Values are presented mean ± standard deviation, median (range), and n (%). BMI: Body mass index, COVID-19: Coronavirus disease-2019, FMF: Familial Mediterranean fever

were Turkish and 11 (6.63%) were ethnically Arabic, while in the symptomatic group 80 (96.38%) were Turkish and 3 (3.62%) were Arabic. There was no significant difference between the nationalities of the pregnant women in the two groups (p=0.333). There was no significant difference between blood groups (p=0.403) or rhesus (Rh) factor status (p=0.894) between the groups. The two groups did not differ for gravida (p=0.091), parity (p=0.133) or history of abortion (p=0.196).

Gestational weeks of pregnancies in the symptomatic group were lower than in the asymptomatic group (p<0.001) (Table 2). The preterm birth rate in the symptomatic group was 48.2% (n=40), significantly higher than the asymptomatic group where it was 14.5% (n=24) (p<0.001). Premature rupture of membranes (PROM) developed more frequently in asymptomatic pregnant women (p<0.001). The vaginal delivery rate was higher in asymptomatic pregnant women, while the cesarean section rate was higher in symptomatic pregnant women (p=0.01). Both maternal ICU admission and maternal death were significantly higher in symptomatic pregnant women (p<0.001). All of the pregnant women in the symptomatic group were diagnosed with COVID-19 pneumonia by thorax CT and 78 (94%) by LUS (p<0.001).

Symptomatic women had a higher rate of leukocytosis (p<0.001) and lymphopenia (p<0.001) than asymptomatic patients. Other laboratory parameters, such as CRP (p<0.001), alanine aminotransferase (ALT) levels (p=0.018), aspartate aminotransferase (AST) levels (p=0.01), blood urea nitrogen (BUN) (p<0.001), creatinine (CR) levels (p=0.029), and

Table 2. Comparison of maternal obstetric characteristics with symptomatic status

	Asymptomatic (n=166)	Symptomatic (n=83)	p
Gestational hypertension	2 (1.2)	0 (0)	0.554
Gestational diabetes mellitus	7 (4.2)	4 (4.8)	0.829
Gestational age (week)	38.10±1.87	35.61±3.47	**<0.001**
Preterm birth (<37 week)	24 (14.5)	40 (48.2)	**<0.001**
Spontaneous	10 (6.02)	4 (4.83)	0.689
Iatrogenic	14 (8.43)	36 (43.37)	**<0.001**
Premature rupture of membranes	24 (14.5)	2 (2.4)	**<0.001**
Mode of delivery			**0.01**
Vaginal	73 (43.97)	23 (27.72)	
Cesarean section	93 (56.03)	60 (72.28)	
Maternal ICU	1 (0.6)	40 (48.2)	**<0.001**
Maternal death	0 (0)	18 (21.7)	**<0.001**
Maternal transfusion	5 (3)	10 (12)	**0.002**
Thoracic CT - COVID-19 pneumonia	51 (30.7)	83 (100)	**<0.001**
LUS - COVID-19 pneumonia	62 (37.3)	78 (94)	**<0.001**

Values are presented mean ± standard deviation and n (%). ICU: Intensive care unit, COVID-19: Coronavirus disease-2019, CT: Computed tomography, LUS: Lung ultrasonography

international normalized ratio values (p=0.013) were also significantly higher in symptomatic pregnant women (Table 3). When the results of newborn parameters were evaluated, birth weight (p<0.001), newborn length (p=0.001), newborn head circumference (HC) (p<0.001), 1 minute Activity pulse grimace appearance respiration (APGAR) score (p=0.016), and 5 minute APGAR score (p=0.012) was lower in symptomatic women. The neonatal intensive care unit (NICU) admission rate was higher in symptomatic pregnant women (p<0.001). The rates of indications for NICU admission, including respiratory distress (p=0.009) and prematurity (p=0.012), were higher in the symptomatic group (Table 4).

The delivery rate due to the indication of maternal general condition disorder was higher in the symptomatic group (p<0.001). The birth rate due to PROM (p=0.002), elective cesarean section (p=0.007), and pregnant in term action (p=0.002) was higher in the asymptomatic group (Table 5).

A logistic regression model was developed to assess risk factors in women within the symptomatic group. This showed that symptomatic infection was associated with an increased risk of iatrogenic preterm birth [odds ratio (OR): 8.31, 95% confidence interval (CI): 4.13-16.72; p<0.001] cesarean section (OR: 2.04, 95% CI: 1.15-3.62; p=0.013), maternal death (OR: 1.27, 95% CI: 1.14-1.43; p<0.001), and NICU admission (OR: 4.81, 95% CI: 2.26-8.69; p<0.001) (Table 6).

Discussion

The first COVID-19 case was seen in Turkey on March 11, 2020. On the same date, the World Health Organization declared the coronavirus a pandemic (5). During the course of the pandemic, 102,174 (0.12%) people died due to COVID-19 in Turkey in three years (6). In the present study, the clinical progression of SARS-CoV-2 positive pregnant women according to their symptomatic status was investigated. We found a relatively high rate of asymptomatic pregnant women (n=166, 66.6%). In the study of Vousden et al. (7), the rate of asymptomatic women was 66% and in the systematic review by Allotey et al. (4), the rate of asymptomatic pregnant women was 54-77%. The high rate of asymptomatic patients has been associated to the vaccines developed against COVID-19. The severity of the disease decreased with increasing use of the vaccine. We found the mean age of symptomatic women to be significantly higher than asymptomatic women, a finding also reported by Minisha et al. (8). In the present study, it was also shown that the risk of severe diseases rises with advancing age. The escalation in disease severity correlates with the rise in age-related comorbidities, heightened susceptibility to diseases, and the age-associated diminishing of immunocompetence (9). This heightened risk of severe diseases contributes to symptomatic manifestations in patients.

Interestingly, it was observed that pregnant women who contracted COVID-19 exhibited a higher rate of symptomatic cases in 2021 and, conversely, a higher rate of asymptomatic cases in 2022 (p=0.015 and p=0.028, respectively). We attribute this reduction in symptomatic infections among pregnant women in 2022 to the widespread adoption of vaccines. Citizen vaccination programmes against the coronavirus commenced in Turkey in January 2021, with a firm recommendation for pregnant women to receive the vaccine published in June 2021 (10). Despite this recommendation, vaccine hesitancy

Table 3. Comparison of maternal laboratory results with symptomatic status

	Asymptomatic (n=166)	Symptomatic (n=83)	p
Lymphocyte (103/µL)	1.89±0.63	0.70±0.29	**<0.001**
Leukocyte (10^3/µL)	8.32±2.02	16.40±8.92	**<0.001**
Prenatal Hb (g/dL)	11.73±1.43	11.16±1.45	**0.003**
Postnatal Hb (g/dL)	10.37±1.67	10.09±1.59	0.208
Decrease in Hb (g/dL)	1.34±0.99	1.07±0.83	**0.037**
Prenatal hematocrit (%)	35.58±3.80	33.96±3.97	**0.002**
Postnatal hematocrit (%)	31.65±4.12	30.74±4.41	0.110
Decrease in hematocrit (%)	3.94±2.95	3.21±2.54	0.055
C-reactive protein (mg/dL)	1.84±2.53	13.82±12.09	**<0.001**
Alanine aminotransferase (u/L)	17.46±30.01	177.64±605.08	**0.018**
Aspartate aminotransferase (u/L)	25.15±31.82	376.80±1745.38	**0.01**
Blood urea nitrogen (mg/dL)	13.07±5.77	19.86±15.92	**<0.001**
Creatinine (mg/dL)	0.54±0.10	0.69±0.63	**0.029**
Uric acid (mg/dL)	4.46±1.25	4.97±2.16	0.052
INR	0.94±0.08	1.45±1.82	**0.013**

Values are presented mean ± standard deviation. Hb: Hemoglobin, INR: International normalized ratio

Table 4. Comparison of neonatal characteristics with symptomatic status

	Asymptomatic (n=166)	Symptomatic (n=83)	p
Birth weight (g)	3137.74±515.02	2711.73±777.47	**<0.001**
Newborn length (cm)	49.60±2.52	47.64±4.85	**<0.001**
Newborn head circumference (cm)	34.40±1.48	33.18±2.75	**<0.001**
APGAR 1 minute	8 (4-8)	8 (2-8)	**0.016**
APGAR 5 minute	9 (6-9)	9 (5-9)	**0.012**
Fetal gender			0.656
Male	89 (53.61)	42 (50.60)	
Female	77 (46.39)	41 (49.40)	
NICU admission	28 (22.9)	41 (49.4)	**<0.001**
Congenital anomaly	2 (1.2)	0 (0)	0.343
Down syndrome	1 (0.6)	0 (0)	
AVSD	1 (0.6)	0 (0)	
Neonatal COVID-19 test positive	2 (1.2)	0 (0)	0.158
NICU indications			
Respiratory distress	28 (16.9)	27 (32.5)	**0.009**
Sepsis	4 (2.4)	6 (7.2)	0.123
Prematurity	4 (2.4)	10 (12)	**0.012**
Hypoglycemia	2 (1.2)	-	0.158
Hypocalcemia	1 (0.6)	-	0.481
Pyloric stenosis	1 (0.6)	-	0.481

Values are presented mean ± standard deviation, median (range), and n (%). COVID-19: Coronavirus disease-2019, NICU: Neonatal intensive care unit, APGAR: Activity pulse grimace appearance respiration, AVSD: Atrioventricular septal defect

Table 5. Comparison of delivery indications with symptomatic status

	Asymptomatic (n=166)	Symptomatic (n=83)	p
Preeclampsia	4 (2.4)	2 (2.4)	0.988
Oligohydramnios	4 (2.4)	1 (1.2)	0.525
Pregnant in term action	50 (30.1)	11 (13.3)	**0.002**
Premature rupture of membranes	21 (12.7)	2 (2.4)	**0.001**
Preterm delivery	3 (1.8)	4 (4.8)	0.383
Cholestasis	4 (2.4)	2 (2.4)	0.988
Maternal general condition disorder	1 (0.6)	35 (42.2)	**<0.001**
Elective cesarean section	40 (34.1)	8 (9.6)	**0.007**
Labour arrest	5 (3)	1 (1.2)	0.383
Breech presentation	4 (2.4)	4 (4.8)	0.365
Fetal distress	19 (12.6)	13 (15.6)	0.767
Placental abruption	2 (1.2)	-	0.158
Eclampsia	1 (0.6)	-	0.481
Macrosomia	3 (1.8)	-	0.083
Transverse presentation	1 (0.6)	-	0.481
Gestational diabetes mellitus	2 (1.2)	-	0.158

Values are presented n (%)

Table 6. Elevated risk factors among women in the symptomatic group (asymptomatic groups shown for reference)

	Asymptomatic (n=166)	Symptomatic (n=83)	Univariate		
			OR	95% CI	p
Iatrogenic preterm birth					
No	152 (91.57)	47 (56.63)	8.31	4.13-16.72	**<0.001**
Yes	14 (8.43)	36 (43.37)			
Cesarean section					
No	73 (43.97)	23 (27.72)	2.04	1.15-3.62	**0.013**
Yes	93 (56.03)	60 (72.28)			
Maternal death					
No	166 (100)	65 (78.3)	1.27	1.14-1.43	**<0.001**
Yes	0 (0)	18 (21.7)			
NICU admission					
No	138 (77.1)	42 (50.6)	4.81	2.26-8.69	**<0.001**
Yes	28 (22.9)	41 (49.4)			

Values are presented n (%). OR: Odds ratio, CI: Confidence interval, NICU: Neonatal intensive care unit

persisted among pregnant women, resulting in an increase in coronavirus vaccination rates among this demographic in the last half of 2021.

In the present study gestational age at birth was significantly lower and the number of iatrogenic preterm births was significantly higher amongst symptomatic patients compared to asymptomatic women. In a systematic review by Khan et al. (11), the rate of preterm birth was also reported to be higher in symptomatic patients. We distinguished between iatrogenic and spontaneous preterm births. We found that symptomatic COVID-19 infection did not affect the spontaneous preterm birth rate (p=0.689), but significantly increased the iatrogenic preterm birth rate (p<0.001). For women in the symptomatic group, the prominence of vital sign deterioration was attributed to the severity of the disease. To avert fatal consequences in fetuses of mothers with compromised vital functions and to alleviate the physiological burden of pregnancy on the mother, the decision to induce labor was made following the administration of necessary agents for fetal lung maturity. The risk of iatrogenic preterm birth was 8.31 times higher in the symptomatic group in the present study and we believe that the higher rates of iatrogenic preterm birth in the symptomatic group stem from the impairment of the maternal general condition. Many studies in the literature have not distinguished between spontaneous and iatrogenic preterm births.

We found higher cesarean rates in symptomatic women (p=0.01). In the study conducted by Şahin et al. (12), the cesarean delivery rate in pregnant women with COVID-19 was reported to be 66.4%. Metz et al. (13) found that cesarean section rates were higher in severe COVID-19 patients than in asymptomatic patients. During pregnancy, changes in the immune system, diaphragmatic elevation, edema in the respiratory tract and increased oxygen consumption occur. These physiological adaptation mechanisms increase the susceptibility of pregnant women to respiratory tract infections (14). Attempting normal birth in mothers with compromised vital functions is somewhat risky, so in cases where the decision for emergency delivery was taken, a cesarean section was performed. This decision was influenced by an increeased oxygen requirement, worsening respiratory failure, worsening clinical condition, and loss of consciousness. The risk of caesarean section was 2.04 times higher in the symptomatic group in the present study and we attribute this higher cesarean delivery rate in women in the symptomatic group to the development of potentially fatal complications arising from COVID-19 infection.

We found high rates of maternal ICU admission (48.2%) and maternal mortality (21.7%) in the symptomatic group. Similarly, Metz et al. (13), reported maternal ICU admission at 35.5% but lower maternal mortality (4.3%) rates in women with severe COVID-19 infection (10). Hantoushzadeh et al. (15) reported that 77.77% of pregnant women with critical COVID-19 died. Tunç et al. (16), demonstrated that all maternal deaths from COVID-19 infection involved reported symptoms of shortness of breath and cough upon initial hospital admission. The risk of maternal death was 1.27 times higher in the symptomatic group in our cohort. Pregnancy adversely affects COVID-19 progression, maternal ICU requirement and maternal mortality rates increase compared to non-pregnant women (17).

In symptomatic women, COVID-19 pneumonia findings detected by radiological methods were more prevalent than in the asymptomatic group (p<0.001) and were present in 78

(94%) of the pregnant women in the symptomatic group with LUS examination before delivery. The finding of COVID-19 pneumonia was confirmed in all women in the symptomatic group with thorax CT after delivery. The diagnostic efficacy of LUS in detecting radiological manifestations of COVID-19 pneumonia appears to be comparable to that of thoracic CT. Lu et al. (18) reported that the sensitivity of LUS was higher in severe disease. In the study by Karacaer et al. (19), the detection rates for confirmed COVID-19 cases were similar at 74% for thoracic CT and 70% for LUS. We performed LUS on admission in all patients because LUS is easy to apply, does not contain radiation, and allows us to obtain radiological findings at the beginning of the hospitalization. The LUS findings were evaluated without the need for a radiologist. Moreover, the treatment of patients with suspicious LUS findings was started at an early stage of admission.

When we examined the laboratory parameters of the pregnant women, leukocytosis, lymphopenia, and elevated CRP were prevalent in the symptomatic group ($p<0.001$). In the study of Grgić et al. (20), lymphocyte levels were lower and leukocyte and CRP values were higher in symptomatic women. London et al. (21) found lower lymphocyte levels in the symptomatic group. In the study of Grechukhina et al. (22), CRP values were found to be useful parameters in predicting the severity of the disease at the time of admission to the hospital. The coronavirus viral genome and antigenic determinants damage the lymphocyte cell skeleton, leading to disintegration. Infection-induced factors, such as soluble Fas Ligand and vascular cell adhesion molecule-1 and the occurrence of cytokine storm exacerbate lymphopenia by inducing programmed death in lymphocytes. In cases of severe pneumonia, lymphocyte counts decrease even further (23). CRP, an acute-phase reactant, serves as a reliable and well-known biomarker of inflammation. It is typically unmeasureable in healthy individuals, with levels rising in response to viral or bacterial infections, concurrently with leukocytes, as part of the reaction of the immune system to inflammatory stimuli (24).

In the present study, prenatal hemoglobin values were significantly lower in the symptomatic group. A meta-analysis conducted by Taneri et al. (25) also found that hemoglobin levels were lower in patients with severe COVID-19 compared to those with moderate severity. Moreover, it has been observed that clinical conditions necessitating intensive care admission due to COVID-19 are associated with even lower hemoglobin levels (25). The mechanism explaining the association between low hemoglobin and COVID-19 infection focuses on iron metabolism and compromised iron utilization in the body. The increased viral load in COVID-19 prevents iron use in erythrocyte biochemical pathways. In addition, iron is crucial for viral particle biogenesis and virus replication. While the host's natural immunity attempts to restrict the virus from using iron, it can exacerbate the anemia (26). Consequently, hemoglobin levels tend to decrease during viral infections.

There were elevated levels of ALT, AST, BUN, and CR in symptomatic women. Severe COVID-19 is known to increase liver and kidney function biomarkers due to multiple organ involvement. The involvement of these organs is linked to the expression of the angiotensin-converting enzyme 2 (ACE2) receptor. The ACE2 receptor facilitates the entry of SARS-CoV-2 into cells, and its presence in the liver and kidneys leads to viral uptake and organ damage (27). Enzymes surge due to organ damage, and their elevation correlates with the severity of COVID-19. A study, excluding chronic liver patients, demonstrated that liver damage intensifies with the severity of COVID-19 and the emergence of the need for intensive care (28).

In the present study, newborns born to the symptomatic group of women had lower birth weight, length and HC. Jenabi et al. (29) also showed the number of low birth weight newborns to be higher in the symptomatic group. The higher rates of preterm birth in the symptomatic group resulted in lower neonatal anthropometric measurements. Furthermore, NICU requirement was higher in the symptomatic group. In the study conducted by Çelik et al. (30), it was reported that the risk of low birth weight, NICU admission, and prematurity increased in babies of mothers with severe COVID-19. In the present study the risk of NICU admission was 4.81 times higher in the symptomatic group. We also believe that the adverse in-utero environment in symptomatic pregnant women with COVID-19 and iatrogenic preterm births contribute to increased NICU rates (31).

COVID-19 was detected in two (1.2%) newborns in the asymptomatic group of our cohort. No infected newborns were detected in the symptomatic group. Two tests were performed to detect SARS-CoV-2 transmission to newborns in the hospital. The first test was done in the first hour after birth, and the second test was performed 24 hours after birth using the nasopharyngeal swab RT-PCR method. The overall congenital infection rate was 0.81% (n=2). In a systematic review by Allotey et al. (32), the rate of congenital infection was <2%. Vertical transmission was detected at a rate of 1.8% (33). In addition, we think that SARS-CoV-2 is transmitted to the newborn by the fecal-oral route during delivery, droplets during breastfeeding, and may be of nosocomial origin too.

Study limitations

We did not follow up involved women after discharge to monitor possible long-term adverse outcomes. We did not obtain data on the coronavirus variant types and vaccination status of all women. However, we did distinguished between iatrogenic and spontaneous preterm births and found that

symptomatic COVID-19 infection did not affect the spontaneous preterm birth rate, but increased the iatrogenic preterm birth rate.

Conclusion

The severity of COVID-19 increased with age. Iatrogenic preterm births and cesarean sections were more common in symptomatic COVID-19 patients because maternal general condition disorder was more prevalent. NICU admission, maternal ICU admission, and maternal mortality rates were higher amongst women with symptomatic COVID-19 infection. We recommend that clinical follow-up is important and closer follow-up is necessary in these women.

Ethics Committee Approval: *The University of Health Sciences Turkey, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Institutional Ethics Committee approval was granted (approval number: 165, date: 14.12.2022).*

Informed Consent: *Retrospective study.*

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

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Do HPV 16 positive/ASC-H cervical cancer screening results predict CIN 2+ better than other high-risk HPV subtypes?

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Abstract

Objective: To determine whether patients with atypical squamous cells, cannot exclude high grade squamous intraepithelial neoplasia (ASC-H) cytology have a correlation between high-risk human papillomavirus (HPV) type and CIN 2+[1] lesion in final pathology.

Material and Methods: The study was conducted retrospectively, using data from three tertiary gynecologic oncology centers located in various regions of Turkey. Data from 5,271 patients who had colposcopy between January 2003 and January 2021 were analyzed.

Results: A total of 163 patients who had ASC-H cervical cytology test results, based on the Bethesda 2014 classification were eligible, and of these 83 (50.9%) who tested positive for HPV were included in the study. There was no correlation between the occurrence of CIN 2+ lesions and age (p=0.053). If there was any HPV 16 positivity (only HPV 16, HPV 16 and 18, HPV 16 and others) the presence of CIN 2+ lesions in the final pathology increased significantly. In HPV 16 positive ASC-H patients, the probability of CIN 2+ lesions in the final pathology were 72.5% while this rate was 48.1% in HPV 16 negative group (p=0.033).

Conclusion: The guidelines do not provide a comprehensive definition of the role of the HPV test in managing ASC-H. Positive high-risk HPV types, especially HPV 16, together with an ASC-H smear result should bring to mind the possibility of high-grade dysplasia. (J Turk Ger Gynecol Assoc 2024; 25: 90-5)

Keywords: ASC-H, cervical cancer, HPV

[1]CIN 2+ lesions were HSIL (CIN 2/CIN 3), micro-invasive cancer, adenocarcinoma in situ, and cervical cancer.

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Introduction

GLOBOCAN 2020 reported approximately 604,000 new cases of cervical cancer and 342,000 deaths attributed to the disease globally (1). Cervical cancer ranked as the fourth most prevalent cancer among women (2). The global occurrence and mortality rates differ among countries, based on factors such as the presence of cervical cancer screening programs and the frequency of human papillomavirus (HPV) vaccination. The components of cervical cancer screening include cervical cytology and/or testing for oncogenic subtypes of the HPV (3,4). Although an HPV test is first option for cervical screening, triage with cervical cytology is recommended for some subtypes (5). Furthermore, cervical cytology may be the only choice in undeveloped and some developing countries (6). Therefore, cytologic evaluation and management still have an important value in a cervical screening program (6).

The Bethesda 2014 classification uses the term "atypical squamous cells, cannot exclude high grade squamous intraepithelial neoplasia (ASC-H)" to describe cytological specimens that do not meet the necessary criteria for high grade squamous intraepithelial lesion (HSIL), but cannot definitively rule it out (7). Therefore, ASC-H cytology should be considered as suspicious for HSIL. ASC-H cytology results account for 10% of all ASC tests reported (8,9), and can be seen in approximately 0.2-0.3% of all cervical cytology tests (10).

HPV positivity has been reported as 68-84% in ASC-H cases (8,9). The prevalence of cervical intraepithelial neoplasia 2+ (CIN 2+) lesions in cases of HPV positive ASC-H is estimated to be between 30% and 47% (8,11). Nevertheless, the existing literature lacks sufficient evidence concerning the correlation between HPV subtypes and the likelihood of CIN 2+ lesions in ASC-H cytology. The aim of the present study was to assess the correlation between CIN 2+ lesions and high-risk HPV subtypes among patients who presented with HPV-positive ASC-H cytology.

Material and Methods

The study was conducted retrospectively, using data from three tertiary gynecologic oncology centers located in various regions of Turkey. The study was approved by the University of Health Sciences Turkey, Ankara City Hospital Clinical Research Ethics Committee (approval number: 7, date: 29.01.2021). Between January 2003 and January 2021, the data of 5,271 patients who underwent colposcopic examination in the gynecological oncology outpatient clinics of the participating centers were analyzed. Among this cohort, patients who had ASC-H cervical cytology test result were investigated. Patients who had positive HPV test result and ASC-H simultaneously were included. Every patient provided their explicit consent for the institution to utilize their clinical data. The liquid-based thin-layer slide preparation technique was used for all ASC-H cervical cytology. NOVAprep® liquid-based cytology systems (NOVAprep Inc., Russia) and Max-prep® cytology systems (Corebiotech Co., Korea) were used for the liquid-based cytology preparation. The age, HPV test results, and histopathological reports of the colposcopic biopsy and endocervical curettage (ECC) were analyzed. HPV-DNA was isolated by using QIAsymphony® DSP virus/pathogen MIDI kit, HPV-DNA was detected and typed by QIAscreen HPV-PCR kit (Qiagen Inc., Germany). Three tertiary gynecological oncology clinics implemented the American Society for Colposcopy and Cervical Pathology (ASCCP) recommendations for the management of pre-invasive lesions. Colposcopic examination was routinely performed in patients with ASC-H cytology in the centers included in this study. ECC was also performed. Conization was performed in patients who had HSIL, micro-invasive cancer, or adenocarcinoma in situ (AIS) on colposcopic biopsy and who had discordance between biopsy and clinical evaluation. HSIL (CIN 2/CIN 3), micro-invasive cancer, AIS, and cervical cancer were defined as CIN 2+ lesions.

Statistical analysis

The SPSS, version 22.0 was used for all statistical analyses (IBM SPSS Inc., Chicago, IL, USA). Descriptive values are expressed as arithmetic mean ± standard deviation, median and percent. The chi-square test was used to analyze categorical variables. A p-value <0.05 was deemed statistically significant.

Results

There were 163 cases with ASC-H cytology findings, and of these 83 (50.9%) patients who had positive HPV test result and ASC-H simultaneously were included. The mean patient age was 45±9.21 years. HPV 16 was the most prevalent type of HPV. There were 36 patients (43.4%) with HPV 16 only, four patients (4.8%) with both HPV 16 and 18, and eleven patients (13.3%) who had HPV 16 and HPV types other than HPV 18 simultaneously. HPV type was undetermined in five (6%) patients. The patients' characteristics are presented in Table 1.

Colposcopy was performed in all patients. Colposcopic biopsy was performed in 80 patients who had suspicious lesions on colposcopic examination. Colposcopic examinations of the other three patients were normal. HSIL was the most common pathology in 42/80 (52.5%) among the colposcopic biopsy and ECC results of the patients. The remaining diagnoses included squamous cell carcinoma in two patients, micro-invasive cancer in two patients, and AIS in one patient. Conization was performed in 47 patients. Eight patients with HSIL biopsy results refused conization. Among the pathological results of conization, the most common pathology was HSIL in 31/47

(66%). On final pathological diagnosis, CIN 2+ lesion was reported in 51 (61.4%) patients and HSIL was the most common (55.4%) type among these results (Table 1).

The association between CIN 2+ lesions and age or HPV type in patients with ASC-H cytology is summarized in Table 2. The incidence of CIN 2+ lesions was 73% among patients aged <44 years, compared to 52.2% among patients aged ≥44 years (p=0.053). It was significantly more likely that the final pathology would show CIN 2+ lesions in patients who had HPV 16 positivity (only HPV 16, HPV 16 and 18, or HPV 16 and others). The incidence of CIN 2+ lesions, as determined by the final pathological diagnosis, was 72.5% in patients who tested positive for both HPV 16 and had ASC-H cytology simultaneously. In contrast, the incidence was 48.1% in patients who tested positive for a type of HPV other than HPV 16 (p=0.033).

HPV 16 positivity in patients with ASC-H cytology predicted CIN 2+ lesions with 74% specificity, 50% sensitivity, 72.5% positive predictive value, and 51.9% negative predictive value. Statistics were not analyzed for other HPV types excluding HPV 16 because the number of patients for other subtypes was insufficient.

Table 1. Characteristics of entire cohort (n=83)

Characteristics		**Mean ± SD**	**Median (range)**
Age		45±9.21 years	44 (24-66) years
		n	**%**
Age	<25 years	1	1.2
	≥25 years	82	98.8
HPV type	Type 16 only	36	43.4
	Type 18 only	2	2.4
	Types 16 with 18	4	4.8
	Other types	24	28.9
	Type 16 with other types	11	13.3
	Type 18 with other types	1	1.2
	Unknown types	5	6
Colposcopic examination	Normal (no biopsy)	3	3.6
	Abnormal (with biopsy)	80	96.4
Results of pathological reports obtained by colposcopy (n=80)[1]	Benign	15	18.8
	LSIL (CIN 1)	18	22.5
	HSIL (CIN 2)	25	31.3
	HSIL (CIN 3)	13	16.3
	HSIL (undetermined)	4	5
	AIS	1	1.3
	Micro-invasive cancer	2	2.5
	SCC	2	2.5
Histopathological results of conization (n=47)	Benign	9	19.1
	LSIL	6	12.8
	HSIL	31	66
	Cancer	1	2.1
Results of final pathologicaldiagnosis (n=83)	Benign	16	19.3
	LSIL	16	19.3
	HSIL	46	55.4
	Micro-invasive cancer	2	2.4
	SCC	2	2.4
	Adenocarcinoma	1	1.2

[1]Results from 80 patients who underwent colposcopic biopsy and endocervical curettage. SD: Standard deviation, LSIL: Low-grade squamous intraepithelial lesion, CIN: Cervical intraepithelial neoplasia, HSIL: High-grade squamous intraepithelial lesion, AIS: Adenocarcinoma in situ, SCC: Squamous cell cancer, HPV: Human papillomavirus

Table 2. The relationship between final pathological diagnosis and HPV, and age in patients with ASC-H cytology

Parameters		Final pathological diagnosis				p-value
		Benign and LSIL		CIN 2+		
		n	%	n	%	
Age[1]	<44 years	10	27	27	73	0.053
	≥44 years	22	47.8	24	52.2	
HPV 16 (n=78)[2]	Negative	14	51.9	13	48.1	**0.033**
	Positive	14	27.5	37	72.5	

CIN: Cervical intraepithelial neoplasia, CIN 2+ lesions were HSIL (CIN 2/CIN 3), micro-invasive cancer, adenocarcinoma in situ, and cervical cancer, HPV: Human papillomavirus, LSIL: Low-grade squamous intraepithelial lesion, [1]Median value, [2]Five patients with unknown type were excluded, ASC-H: Atypical squamous cells, cannot exclude high grade squamous intraepithelial neoplasia

Pathological findings of the five patients whose final pathological diagnosis was cancer are shown in Table 3. All but one (80%) had HPV 16 positivity and HPV 31 was positive in the other patient. The final pathological diagnosis was that four patients had squamous cell carcinoma, while one patient had adenocarcinoma.

Discussion

In the present study, patients with ASC-H cytology who tested positive for high-risk HPV, specifically HPV 16, had a significantly higher incidence of CIN 2+ lesions. HPV 16 positivity in patients with ASC-H cytology predicted CIN 2+ lesions with good specificity and positive predictive value but only moderate sensitivity and negative predictive value.

ASC-H refers to atypical squamous cells in the cervix that exhibit the features of a focal high-grade intraepithelial lesion, but are not definitive for diagnosis. It is important to manage ASC-H cytology carefully due to this potential presence of a high-grade intraepithelial lesion. The occurrence of CIN 2-3 lesions in patients with ASC-H cytology ranged from 10% to 85% in the biopsy findings reported in the literature (12-17). Galliano et al. (12) found that 63.8% of patients with ASC-H cytology had high-grade intraepithelial lesions, regardless of their HPV status.

Patton et al. (18) highlighted that age was important for the development of dysplasia in ASC-H cases. However, when predicting high-grade dysplasia in individuals with ASC-H cytology, Kietpeerakool et al. (19) did not find a significant difference between women under 40 and those over 40 years. Gilani et al. (20) also found no difference in the risk of both low-grade and high-grade dysplasia between patients under 30 and those over 49 years. The present study also demonstrated that there was no significant disparity in the likelihood of CIN 2+ lesions among patients with ASC-H cytology based on age.

The prevalence of HPV positivity ranges from 38% to 84% among women with ASC-H cytology (8,13,21,22). Chen et al. (22) reported that among patients with positive high-risk HPV test and ASC-H cytology, the occurrence of CIN 2+ lesions was 55%, based on cervical biopsy or loop electrosurgical excisional procedure specimens. In contrast, the incidence was only 9% among those negative for high-risk HPV. These authors found that women who had both positive high-risk HPV and ASC-H cytology were six times more likely to have high-grade dysplasia compared to those who were negative for high-risk HPV (22). The meta-analysis conducted by Xu et al. (9) examined ASC-H triage and found that the high-risk HPV test had a sensitivity of 93% and a specificity of 45% in detecting CIN 2+ lesions. Data from Keiser Permanente Northern California showed that the likelihood of immediate CIN3+ was

Table 3. Clinical-pathological findings of patients with cervical cancer

Patient no	Age	Cytology	HPV type	ECC result	Colposcopic biopsy result	Conization	Conization result	Final pathological diagnosis
1	49	ASC-H	HPV 16	Benign	HSIL (CIN 2)	Performed	Adenocarcinoma	Adenocarcinoma
2	49	ASC-H	HPV 16	Benign	Micro-invasive SCC	Performed	HSIL (CIN 2)	Micro-invasive SCC
3	52	ASC-H	HPV 31	HSIL (CIN 2)	Micro-invasive SCC	Performed	HSIL (CIN 2)	Micro-invasive SCC
4	28	ASC-H	HPV 16	SCC	SCC	Not performed	-	SCC
5	55	ASC-H	HPV 16	Benign	SCC	Not performed	-	SCC

HPV: Human papillomavirus, ECC: Endocervical curettage, HSIL: High-grade squamous intraepithelial lesion, SCC: Squamous cell cancer, CIN: Cervical intraepithelial neoplasia, ASC-H: Atypical squamous cells, cannot exclude high grade squamous intraepithelial neoplasia

26% for patients with HPV positive ASC-H and 3.4% for patients with HPV negative ASC-H (23). However, the cancer risk was approximately same. Therefore, ASCCP 2019 guideline recommended colposcopic biopsy for ASC-H, regardless of HPV status, as was recommended in the earlier 2012 guideline (23,24). However, the new guideline focused on HPV type in the presence of HSIL cytology. Patients who tested positive for HPV 16 and had HSIL cytology had an immediate risk of CIN 3+ greater than 60%. This threshold was established to justify expedited treatment, which consisted of excisional biopsy without colposcopic biopsy for non-pregnant patients aged 25 years and older (23). The present study found that the risk of CIN 2+ lesions increased significantly from 48% to 72.5% in patients who had both ASC-H cytology and a positive high-risk HPV test, specifically for HPV 16 type. The high-risk HPV test, which includes the HPV 16 type, has a sensitivity of 74% and a specificity of 50% for detecting CIN 2+ lesions in patients with ASC-H cytology. Therefore, our findings suggest that expedited treatment may be considered for patients with ASC-H cytology and HPV 16 positivity.

Study limitations

The advantages of our study were that colposcopic and excisional procedures were all performed by gynecological oncology specialists. The patients were followed up by the same clinic. The present study aimed to elucidate the significance of high-risk HPV type in patients presenting with ASC-H cytology, a previously unidentified component of cervical pathological lesions. Pathology samples of the patients were examined by pathologists specialized in gynecological pathology. One of the limitations of our study is its retrospective design. Furthermore, due to the limited sample size, subgroups of other high-risk HPV types, excluding HPV 16 and 18, were not investigated.

Conclusion

Patients with ASC-H cytology should be managed carefully. This finding has a strong correlation with dysplasia at any level, and particularly with high-grade dysplasia. The HPV type is not fully defined in the management of ASC-H in the literature. The presence of positive high-risk HPV and ASC-H cytology significantly increased the risk of CIN2+ lesion in our cohort. Furthermore, this risk was increased over the 60% in the presence of HPV 16 positivity for ASC-H cytology. Therefore, the expedited treatment can be kept in mind for patients with ASC-H cytology and concurrent HPV 16 positivity. Nevertheless, additional research, especially with larger sample sizes, is necessary to draw definitive conclusions.

Ethics Committee Approval: *The study was approved by the University of Health Sciences Turkey, Ankara City Hospital Clinical Research Ethics Committee (approval number: 7, date: 29.01.2021).*

Informed Consent: *It was obtained.*

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The effect of stress incontinence and pelvic organ prolapse surgery on sexual function and quality of life

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Abstract

Objective: The objective of this study was to evaluate the sexual function and quality of life in female patients diagnosed with stress urinary incontinence (SUI) and pelvic organ prolapse (POP) after undergoing transobturator tape (TOT) or TOT with POP surgery and perineoplasty.

Material and Methods: This prospective study population (n=86) consisted of sexually active women who had been diagnosed with SUI. Forty-six patients diagnosed with SUI with no POP (group 1) underwent TOT procedure only. Forty patients had a diagnosis of stage 2 and higher POP, based on POP quantification system with SUI (group 2). The second group was randomized as TOT-POP surgery (n=20) and TOT-POP surgery with perineoplasty (n=20). Prior to and six months after the surgical procedure, all female participants underwent assessment using the validated Urinary Distress Pre-Operative Inventory (UDI-6), Incontinence Impact Questionnaire (IIQ-7), and Pelvic Organ Prolapse Incontinence Sexual Questionnaire (PISQ).

Results: Post-operative IIQ-7 and UDI-6 scores were significantly lower for all three groups compared to the preoperative period, while a significant increase was observed in PISQ scores ($p<0.01$). The dissimilarity in preoperative and postoperative IIQ-7 and UDI-6 scores exhibited comparable results across the groups, whereas the variance in PISQ scores was notably greater in the TOT + POP surgery + perineoplasty group ($p=0.03$).

Conclusion: Women with SUI or SUI with POP have better quality of life and sexual dysfunction after surgery. Perineoplasty may enhance sexual life in patients with perineal defect and vaginal enlargement. (J Turk Ger Gynecol Assoc 2024; 25: 96-101)

Keywords: Pelvic organ prolapsus, perineoplasty, quality of life, stress urinary incontinence, transobturator tape

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Introduction

Currently, there exists an increasing recognition and fascination surrounding the notion that sexual well-being is an essential element of women's health. In addition, it is widely acknowledged that sexuality plays a significant role in determining one's overall quality of life (1). Several studies have demonstrated that pelvic floor disorders (PFDs), including symptomatic pelvic organ prolapse (POP) and stress urinary incontinence (SUI), have a negative impact on women's sexual well-being and overall quality of life (2-4). The primary challenges encountered by women with PFDs in their sexual lives involve abstaining from sexual intercourse and experiencing sexual dysfunction. These dysfunctions commonly manifest as reduced libido, complaints of vaginal dryness, and dyspareunia (4,5). One frequently observed concern that affects the sexual function of females is perineal trauma, which arises from neurologic and vascular dysfunction of the perineal muscles. This type of dysfunction has the potential to compromise the muscular integrity following vaginal delivery and episiotomies conducted during the

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process of labor (6,7). Perineoplasty is a surgical procedure designed to address perineal abnormalities, with a particular focus on those that occur following childbirth. The present procedure entails the restoration of the perineal musculature and the rectification of the anatomical anomaly situated within the perineal region (8,9).

The surgical repair of POP is commonly linked to enhancements in sexual dysfunction and dyspareunia rates, despite the presence of variations in the anatomical presentation of the prolapsed vagina and the surgical interventions employed (10,11). The effects of surgical intervention on female sexual function in cases of SUI demonstrate a certain degree of variability. However, the majority of women report either no change or improvement in sexual function following the implementation of various urinary incontinence procedures (12-16).

Following a vaginal delivery, certain women may experience vaginal enlargement and deformity as a result of severe perineal tears, inadequately repaired episiotomy procedures, or diminished pelvic support (17). Despite its frequent application and relatively low complication rate, there is currently a lack of consensus on the standard surgical approach and indications for perineoplasty (18-20). Furthermore, the current body of literature exhibits a dearth of studies investigating the effects of perineoplasty surgery on female sexual function. There has been a scarcity of research focused solely on investigating the effects of perineoplasty, a surgical intervention designed to address perineal trauma arising from vaginal childbirth, on the sexual functioning of women (21,22).

The primary aim of this study was to evaluate the sexual functioning and quality of life in women suffering from SUI and POP following transobturator tape (TOT) surgery, as well as TOT combined with POP surgery and/or perineoplasty. The secondary objective was to conduct a comparative analysis of these procedures to examine potential disparities in sexual function and quality of life assessments.

Material and Methods

A prospective cohort study was undertaken at our tertiary university referral hospital from February 2020 to December 2021. Approval for the research was obtained from both the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Institutional Review Board and Local Ethics Committee of the study site (approval number: 2020-04-16, date: 17.02.2020). The study included individual participants who provided informed consent. The study recruited a total of 86 sexually active women who had been diagnosed with SUI through urodynamic examination. The recruitment process was non-randomized and took place at an outpatient clinic. Among them, 46 patients diagnosed with SUI with no POP underwent a TOT procedure only (group 1) and 40 had a diagnosis of stage 2 and higher POP, based on the pelvic organ prolapse quantification (POP-Q) system (23), with SUI. This group (n=40) was randomized; one half (n=20) underwent TOT-POP surgery (group 2), while the other half (n=20) underwent TOT-POP surgery with perineoplasty (group 3). The surgeries we performed within the scope of POP surgery were lateral suspension, sacrohysteropexy, sacrocolpopexy, sacrouterine plication, with abdominal hysterectomy or not, and colporrhaphy anterior-posterior, high MacCall, and sacrospinous fixation with vaginal hysterectomy or not. We did not use transvaginal mesh except in TOT for POP surgery.

Women who had previously undergone POP or incontinence surgery, previously been diagnosed with sexual dysfunction, received hormone replacement therapy, and/or used drugs that could affect sexual function, such as antidepressants, antipsychotics, and beta-blockers, were excluded from the study. During the preoperative evaluation, the patients' ages, body mass indexes (BMI), educational status, number of births, delivery types, menopausal status, and medical history were recorded. A detailed physical examination was performed, including transvaginal examination, stress test, and POP evaluations based on the POP-Q system (23). Transvaginal ultrasound was also performed to measure urethral length and to detect pelvic pathologies. A filling cystometry and pressure flow study were conducted in all patients in accordance with good urodynamic practice of the International Continence Association (24), and all women completed the validated version of Urinary Distress Pre-Operative Inventory (UDI-6), Incontinence Impact Questionnaire (IIQ-7), and the Pelvic Organ Prolapse Incontinence Sexual Questionnaire (PISQ) prior to the surgery (25,26). They were re-evaluated at least six months postoperatively by UDI-6, IIQ-7, and PISQ questionnaires, and stress test. A vaginal examination was performed to assess the complications, and transvaginal ultrasonography was performed to evaluate mesh location and the ratio between the mesh-urethra distance and the urethral length in order to optimally perform midurethral mesh placement during surgery.

Statistical analysis

The statistical analysis was conducted using the NCSS 2007 program (Kaysville, Utah, USA). The study data was analyzed using descriptive statistical techniques such as mean, standard deviation, median, frequency, percentage, minimum, and maximum. Shapiro-Wilk and graphical analysis assessed quantitative data for normal distribution. Quantitative variables with non-normal distribution were compared using Mann-Whitney U test. Kruskal-Wallis and Dunn-Bonferroni tests were used to compare more than two groups of non-normal quantitative data. Comparing qualitative data used the

Pearson's chi-square and Fisher-Freeman-Halton exact tests. Statistical significance was set at $p<0.05$.

Results

This study included 86 women with a mean age of 54±8 years, ranging from 40-72 years. TOT was used in 53.4% (n=46), TOT + POP surgery in 23.2% (n=20), and TOT + POP surgery + perineoplasty in 23.2% (n=20) of the study participants.

Bladder injury occurred in 1 (1.3%) during the operation. De novo urgency and recurrent SUI developed in 15.1% (n=13), while mesh erosion was observed in 2 (2.3%) in the late period.

The urethra length of the cases ranged from 30 to 54 mm with a mean of 38±5.1 mm, the distance between the mesh and distal urethra was between 12 and 30 mm (mean; 19.2±3.7 mm), and the ratio of the mesh-urethra distance and urethral length ranged from 0.3 to 0.8 (mean; 0.5±0.1).

The demographic characteristics of the cases are shown in Table 1, 2. Operation type did not differ by age, BMI, education, parity, or delivery type ($p>0.05$). However, in the assessment of menopausal status, surgical menopause was more prevalent in the TOT + POP surgery group ($p=0.03$). Late complications, subjective operation satisfaction, postoperative stress test ratio, preoperative doing regular Kegels exercise, urethra lengths, and mesh urethra/urethra length ratio did not differ by operation type ($p>0.05$). As shown in Table 3, when the pre- and postoperative six-month IIQ-7, UDI-6, and PISQ scores were compared by operation type, no significant difference was found ($p>0.05$). However, when comparing the preoperative IIQ-7 and UDI-6 scores with the postoperative IIQ-7 and UDI-6 scores for all three groups, a significant decrease was detected, while a significant increase was found in the PISQ scores ($p<0.01$). When the difference in the scores of IIQ-7 and UDI-6 was evaluated, there was no significant difference between the groups ($p=0.11$ and $p=0.14$ respectively). However, when the difference in scores of PISQ was evaluated, it was significantly increased in group 3 ($p=0.03$). No significant difference was observed between the ratio of mesh-urethra distance and urethral length according to the operation satisfaction levels of the study participants ($p=0.18$). Furthermore, there was no significant difference between the distribution of satisfaction levels with the operation according to urinary incontinence during sexual intercourse ($p=0.08$). No significant difference was observed between the distribution of the satisfaction levels of the operation according to the participants experiencing negative feelings such as fear, embarrassment, disgust, or guilt during sexual intercourse ($p=0.20$), as shown in Table 4.

Discussion

An improvement in postoperative quality of life and sexual life across all three groups undergoing surgery for SUI and

Table 1. Characteristics of the study groups

		TOT (n=46)	TOT + POP surgery (n=20)	TOT + POP surgery + perineoplasty (n=20)	p
Age (years)	Median (min.-max.)	52 (41-72)	56 (40-70)	55 (45-72)	0.21
BMI (kg/m^2)	Median (min.-max.)	31.2 (21-47.6)	30.7 (22-43.9)	31.2 (22.9-41.7)	0.71
Education status	Literate	8 (17%)	2 (10%)	4 (20%)	
	Primary school	26 (57%)	14 (70%)	12 (60%)	
	Middle school	4 (9%)	2 (10%)	3 (15%)	
	High school	8 (17%)	2 (10%)	1 (5%)	0.62
Parity	Median (min.-max.)	3 (1-8)	3 (2-7)	3 (2-9)	0.17
	1 birth	2 (4%)	0 (0%)	0 (0%)	
	2 births	18 (39%)	4 (20%)	4 (20%)	
	3 births	12 (26%)	11 (55%)	8 (40%)	
	≥4 births	14 (30%)	5 (25%)	8 (40%)	0.24
Delivery type	Vaginal	42 (91%)	15 (75%)	17 (85%)	
	Abdominal	2 (4%)	0 (0%)	0 (0%)	
	Vaginal + abdominal	2 (4%)	5 (25%)	3 (15%)	0.10
Menopausal status	Premenopause	9 (20%)	1 (5%)	3 (15%)	
	Menopause	28 (61%)	13 (65%)	17 (85%)	
	Surgical menopause	5 (11%)	6 (30%)	0 (0%)	
	Perimenopause	4 (9%)	0 (0%)	0 (0%)	**0.03**

Bold values are statistically significant at $p<0.05$. TOT: Transobtrator tape, POP: pelvic organ prolapsus, BMI: Body mass index, min.: Minimum, max.: Maximum

Table 2. Comparisons of data according to operation types

		TOT (n=46)	TOT + POP surgery (n=20)	TOT + POP surgery + perineoplasty (n=20)	p
Early and late complications	No	38 (83%)	16 (80%)	17 (85%)	
	Yes	8 (17%)	4 (20%)	3 (15%)	0.56
Subjective postoperative satisfaction	Good	32 (70%)	12 (60%)	15 (75%)	
	Not bad	8 (17%)	6 (3%)	3 (15%)	
	Bad	6 (13%)	2 (10%)	2 (10%)	0.75
Stress test at 6 months postoperatively	Negative	38 (83%)	19 (95%)	20 (100%)	
	Positive	8 (17%)	1 (5%)	0 (0%)	0.07
Preoperative doing regular Kegel exercise	Yes	38 (83%)	19 (95%)	18 (90%)	
	No	8 (17%)	1 (5%)	2 (10%)	0.55
Kegel exercise before operation (month)	N	40	17	18	
	M (min.-max.)	6 (3-6)	6 (3-6)	6 (2-6)	0.63
Urethral length	M (min.-max.)	39 (30-54)	37.5 (30-46)	38.5 (30-47)	0.60
Mesh urethra/urethral length		0.5 (0.3-0.7)	0.5 (0.3-0.8)	0.5 (0.4-0.8)	0.47
M, median, TOT: Transobturator tape, POP: Pelvic organ prolasus, min.: Minimum, max.: Maximum					

Table 3. Comparisons of the pre- and postoperative six-month IIQ-7, UDI-6, and PISQ scores according to operation types

	TOT (n=46) Median (min.-max.)	TOT + POP surgery (n=20) Median (min.-max.)	TOT + POP surgery + perineoplasty (n=20) Median (min.-max.)	p
Preoperative IIQ-7	9 (2-18)	7 (2-16)	12 (1-17)	0.08
Postoperative IIQ-7	1 (0-18)	3 (0-11)	0 (0-17)	0.48
	p=0.001	**p=0.003**	**p=0.004**	
Δ IIQ7	6.5 (-13-18)	4 (-6-14)	7 (-4-17)	0.11
Preoperative UDI-6	9 (3-15)	9 (2-11)	9.5 (4-16)	0.09
Postoperative UDI-6	3 (0-12)	4 (0-9)	4 (0-9)	0.5
	p=0.001	**p=0.001**	**p=0.002**	
Δ UDI-6	5 (-8-12)	5 (-3-8)	5.5 (-4-16)	0.14
Preoperative PISQ	27.5 (13-40)	27.5 (18-37)	22.5 (5-37)	0.13
Postoperative PISQ	32.5 (17-40)	30 (21-39)	34 (29-40)	0.10
	p=0.001	**p=0.03**	**p=0.001**	
Δ PISQ	-4 (-17-9)	-3.5 (-15-8)	-7 (-35-0)	**0.03**
Bold values are statistically significant at p<0.05. UDI-6: Urinary Distress Pre-Operative Inventory, IIQ-7: Incontinence Impact Questionnaire, PISQ: Pelvic Organ Prolapse Incontinence Sexual Questionnaire, min.: Minimum, max.: Maximum, TOT: Transobturator tape, POP: Pelvic organ prolasus				

POP was observed. However, there was a notable significant difference in augmentation in sexual life score reported by the patients where perineoplasty was incorporated alongside TOT and POP surgery, in comparison to the remaining two groups. This suggests that the inclusion of perineoplasty alongside TOT and POP surgery in individuals with perineal defects can significantly enhance sexual quality of life at or after the six-month mark following surgery. Stress incontinence, POPs, and wide vagina association are common due to the similar etiology. Females experiencing the perception of a broad vaginal canal may express dissatisfaction with reduced friction during sexual intercourse and a decline in sexual gratification. In TOT-treated SUI patients, quality of life and sexual life scores increased dramatically after the sixth postoperative month. Although a small proportion of earlier studies reported that sexual life worsened because of dyspareunia after SUI surgery, most found that sexual life scores improved or did not change (12,15,16,27,28). A meta-analysis of a secondary analysis of the Stress Incontinence Surgical treatment efficacy trial and trial of mid-urethral slings found that women who underwent anti-incontinence surgery had improved sexual function from baseline to 24 months post-surgery. Although surgical

Table 4. The relationship of subjective postoperative satisfaction with incontinence and negative emotional reactions during sexual intercourse and mesh urethra/urethral length ratio

Subjective postoperative satisfaction levels					
		Good (n=59)	**Not bad (n=17)**	**Bad (n=10)**	**p**
Mesh-urethra distance/urethral length	Median (min.-max.)	0.5 (0.3-0.8)	0.5 (0.4-0.6)	0.5 (0.3-0.7)	0.18
Are you incontinent of urine (leak urine) with sexual activity?	Always	12 (20%)	2 (12%)	0 (0%)	
	Usually	14 (24%)	1 (6%)	1 (10%)	
	Sometimes	7 (12%)	2 (12%)	4 (40%)	
	Rarely	3 (5%)	0 (0%)	1 (10%)	
	No	23 (39%)	12 (70%)	4 (40%)	0.08
When you have sex with your partner, do you have negative emotional reactions such as fear, disgust, shame or guilt?	Always	0 (0%)	0 (0%)	0 (0%)	
	Usually	17 (29%)	3 (17%)	1 (10%)	
	Sometimes	20 (34%)	2 (12%)	6 (60%)	
	Rarely	6 (10%)	1 (6%)	0 (0%)	
	No	16 (27%)	11 (65%)	3 (30%)	0.20

procedures vary, most improvement happens in the first 12 months and persists for 24 months (28).

As pelvic organs prolapse from different anatomical regions of the vagina, such as anterior, apical, posterior, or combined, surgical repair types (abdominal, vaginal, natural tissue, synthetic mesh) also vary. However, several studies have shown that surgical repair of POP results in improvement in sexual dysfunction and dyspareunia, similar to our study results (10,29-31). After anterior repairs, uterosacral suspensions, sacrospinous suspensions, and sacrocolpopexy, PISQ-12 scores increased in a 2020 systematic analysis of 67 research articles. However, the scores did not change after posterior repairs and surgeries in which transvaginal mesh and biological grafts were applied (32). Similarly, the results of the CARE study evaluating the effect of abdominal sacrocolpopexy on sexual function reported that mean PISQ scores increased one year after the surgery (11).

Perineoplasty may help women who suffer sexual dysfunctions after vaginal delivery (21). Perineoplasty can alleviate the sensation of a wide vagina with minimal complication rates and excellent patient satisfaction (22). Another study revealed that sexual satisfaction significantly increased in women with vaginal laxity six and 18 months after colpoperineoplasty (11,33). The findings of the present study revealed that adding perineoplasty to TOT and POP surgery appeared to improve the quality of sexual life much more in the sixth postoperative month, similar to the results of these earlier studies.

The low case count and PISQ-12's sexual dysfunction assessment may be limitations of this investigation. PISQ-12 measures sexual function well, but it does not examine partner-related issues and so sexual dysfunction cannot be fully understood. The IUGA-revised Pelvic Organ Prolapse/Incontinence Sexual Questionnaire (PISQ-IR) in Turkish is not valid or accurate. The PISQ-IR questionnaire was unavailable for our investigation.

Conclusion

When women with a diagnosis of SUI and/or POP with SUI are treated with an appropriate surgical method, their quality of life increases, and their sexual dysfunctions improve.

Ethics Committee Approval: *The study was approved by the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (approval number: approval number: 2020-04-16, date: 17.02.2020).*

Informed Consent: *The study included individual participants who provided informed consent.*

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The effect of dienogest treatment on anti-Mullerian hormone in patients with endometrioma: a 12-month follow-up study

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Abstract

Objective: To assess the effect of dienogest treatment on endometrioma (OMA) size, serum anti-Mullerian hormone (AMH) levels and associated pain over a 12-month follow-up period.

Material and Methods: A longitudinal cohort study of 104 patients with OMA who were treated with dienogest, between January 2017 and January 2020. Of the included patients, each had a 12-month follow-up period with transvaginal or pelvic ultrasound and measurement of serum AMH concentration at the sixth and twelfth months of follow-up. The alteration in OMA size in the sixth and twelfth months of treatment was the primary outcome measure and the alteration in AMH concentration over the same period was the secondary outcome measure. The only exclusion criterion was having surgical intervention for OMA during the follow-up period (n=44). In patients with bilateral OMA (n=21), the change in size of the largest OMA was considered in the analysis.

Results: A total of 60 patients with a mean ± standard deviation (SD) age of 31.5±8.0 years were included. The mean ± SD OMA size on the day the dienogest was started was 46.3±17.4 mm and the mean AMH level was 3.6±2.4 ng/mL. After six months, the mean OMA size had decreased to 38.6±14.0 mm, with a median difference of 7.8 mm [95% confidence interval (CI): 3.0 to 12.6; p=0.003]. The mean AMH level was 3.3±2.7 ng/mL at 6 months follow-up (95% CI: -0.2 to 0.8; p=0.23) and the average difference was 0.3 ng/mL. At the 12th-month visit, when compared with the beginning of the treatment, OMA size had again significantly decreased by a median of -8.9 mm (95% CI: -2.9 to -14.9; p=0.005), and the decline in median AMH was also significant (-0.9 ng/mL, 95% CI: -0.1 to -1.7; p=0.045). The initial mean ± SD visual analog scale pain score at the commencement of dienogest treatment was 6.3±3.4. The mean values at the sixth and twelfth months of dienogest therapy were 1.08±1.8 and 0.75±1.5, respectively (both p<0.001 compared to baseline).

Conclusion: At the sixth and twelfth months of dienogest treatment a significant decrease in OMA size and reported pain scores were observed, whereas the AMH concentrations did not change significantly. (J Turk Ger Gynecol Assoc 2024; 25: 102-6)

Keywords: Endometrioma, anti-Mullerian hormone, dienogest, pelvic pain, ovarian reserve

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Introduction

Endometriosis is a chronic disorder that affects approximately 2-10% of women throughout the reproductive years (1,2). Whereas endometriosis is often associated with pain-related symptoms, including dysmenorrhea, dyspareunia, and dyschezia, a significant portion of women do not have any symptoms (3,4). Among patients with endometriosis, 17-44% may have visible ovarian endometrioma (OMA) on ultrasonography (US) that represents a more severe stage of the disease, according to the revised American Society of Reproductive Medicine staging (5,6). OMA may be associated

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with infertility and hence approximately 40% of infertile women with endometriosis are reported to have visible OMA cysts (7).

The optimal management of OMA during the reproductive years is controversial. The preferred strategy depends on the patient's age, desire for childbearing, severity of pain-related symptoms, presence of bilaterality, and suspicion of malignancy (8,9). Given the high success rate for pain-related symptoms and lack of any harm to the ovarian reserve, medical treatments may be considered in patients with moderate-severe symptoms who do not have any desire to preserve fertility. Among the available medical treatment options, combined contraceptive pills or progestin-only drugs, with or without non-steroidal anti-inflammatory drugs, may be the first choice due to the low complication rate and high patient compliance (10). Although dienogest is one of the options within the group of progestin-only drugs, there are constrained statistics approximately its effect on the scale of the OMA and therefore serum anti-Mullerian hormone (AMH) concentration in the course of 365 days of compliance with up.

In the present study, the aim was to investigate if there were statistically significant changes in the volume of OMA, AMH levels and associated symptoms at one-year follow-up in patients with OMA on dienogest.

Material and Methods

Patients and study design

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee (approval number: 2021/09-30, date: 20.04.2021). Informed consent was obtained from all patients participating in the study.

In the current observational cohort study, consecutive patients with a diagnosis of OMA and treated with dienogest (Visanne, Bayer, İstanbul, Turkey) between January, 2017 to January, 2020 at university department of obstetrics and gynecology were recruited. The inclusion criteria were being between the ages of 20 and 45 years, no patient desire to preserve fertility, and the preferred medical treatment was dienogest alone. The exclusion criteria were history of any surgical treatment (cystectomy, cyst aspiration/fenestration or sclerotherapy) before the study period, use of the combined contraceptive pill in the three months preceding the study and suspicious of malignancy as suggested by US.

All included patients received 2 mg orally dienogest per day for at least 12 months. Data concerning the largest OMA cyst diameter on US, serum AMH measurement and visual analog scale (VAS) from 0 to 10 (0: no pain to 10: unbearable pain) were collected. Patients were asked about pelvic pain (dysmenorrhea, or non-cyclic pelvic pain) at the beginning, sixth, and twelfth months of dienogest treatment. Serum AMH was measured with the Elecsys AMH assay (Roche Diagnostic International, IN, USA.) All examination with US was conducted by a single physician (G.B.).

Statistical analysis

A retrospective analysis of prospectively collected data was conducted using SPSS, version 23 (IBM Inc., Chicago, IL, USA). The paired t-test was employed to compare numerical values, and a statistical significance level of $p<0.05$ was used.

Results

Of 104 patients, 44 (42.3%) were excluded and 60 patients were analyzed. The mean ± standard deviation (SD) of age was 31.5±8.0 years. Demographics of the study population are presented in Table 1. At the start of dienogest treatment, the mean largest diameter of the OMAs was 46.3±17.4 mm, and the mean serum AMH concentration was 3.6±2.4 ng/mL. The main symptoms observed among patients were: dysmenorrhea (26.7%), chronic pelvic pain (41.7%), and menstrual irregularity (13.3%). A total of 30% of the patients did not exhibit any symptoms.

After six months of treatment, the mean OMA size decreased to 38.6±14.0 mm, with a mean difference of 7.8 mm

Table 1. Study population characteristics at baseline

Characteristics	
Number of patients	60
Age, years	31.5±8.0
Body mass index, kg/m^2	23.4±4.0
Symptoms, n (%)	
Dysmenorrhea	16 (26.7)
Chronic pelvic pain	25 (41.7)
Menstrual irregularity	8 (13.3)
Asymptomatic	18 (30.0)
VAS score at baseline	6.3±3.4
Ultrasound type, n (%)	
Transvaginal	32 (53.3)
Pelvic ultrasound	28 (46.7)
Baseline endometrioma size, mm	46.3±17.4
Patients with bilateral endometrioma, n (%)	21 (35%)
Baseline AMH, ng/mL	3.6±2.4
VAS: Visual analog score, AMH: Anti-Mullerian hormone	

Table 2. Comparison of mean endometrioma diameters, AMH levels and VAS scores at baseline, six months, and 12 months of treatment with dienogest

Measurements	Baseline	6 months	Percentage change in mean value	p at six-months versus baseline*	12 months	Percentage change in mean value	p-value 12 months versus baseline*
Endometrioma diameter (mm)	46.3±17.4	38.6±14.0	16.6	0.003	37.5±15.7	19	0.005
AMH level (ng/mL)	3.6 ± 2.4	3.3±2.7	8.3	0.23	2.7±1.9	25	0.045
Endometriosis-related VAS pain score	6.3±3.4	1.08±1.8	82.8	0.001	0.75±1.5	88.1	0.001

*Student's t-test, values are presented as mean ± standard deviation. AMH: Anti-Mullerian hormone, VAS: Visual analog scale

[95% confidence interval (CI): 3.0 to 12.6; p=0.003]. The mean AMH level was 3.3±2.7 ng/mL, with a mean difference of 0.3 ng/mL (95% CI: -0.2 to 0.8; p=0.23).

After 12 months of treatment, the mean OMA diameter was 37.5±15.7 mm, with a mean difference of 8.9 mm (95% CI: 2.9 to 14.9; p=0.005). Similarly, the mean AMH concentration was 2.7±1.9 ng/mL, with a mean difference of 0.9 ng/mL (95% CI: 0.1 to 1.7; p=0.045) at 12 months compared to baseline. However, there was no significant difference in the OMA diameter or AMH concentration between the sixth and twelfth months of treatment measurements. OMA size at baseline, six, and twelve months of dienogest treatment was presented in Figure 1.

Serum AMH concentration at baseline, six, and twelve months of dienogest treatment was shown in Figure 2.

In the study population, at the beginning of the dienogest treatment, mean ± SD VAS score was 6.3±3.4. There was a significant improvement in VAS scores at both the sixth and twelfth months compared to baseline (1.08±1.8; p<0.001 and 0.75±1.5; p<0.001, respectively). Table 2 presents the changes in the OMA dimensions, AMH levels and endometriosis-related VAS pain score at baseline, six, and 12 months.

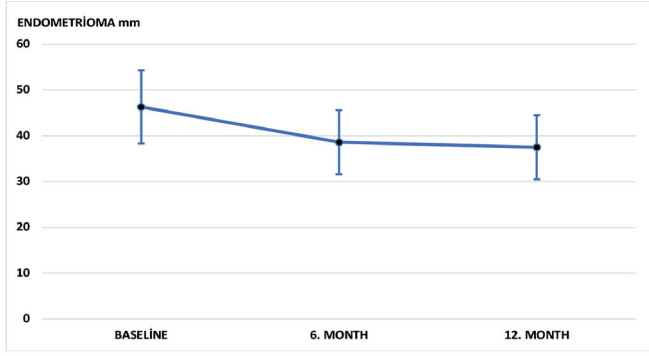

Figure 1. OMA size (mm) at baseline, six, and twelve months of dienogest treatment (mean ± SD)
OMA: Endometrioma, SD: Standard deviation

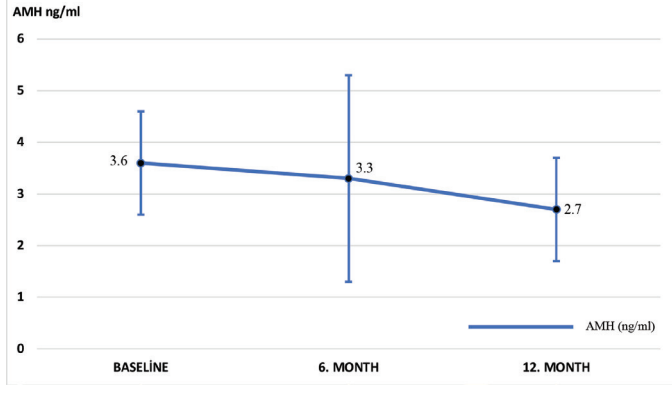

Figure 2. Serum AMH (ng/mL) concentration at baseline, six, and twelve months of dienogest treatment (mean ± SD)
AMH: Anti-Mullerian hormone, SD: Standard deviation

Discussion

In the current study, there was a significant decrease in the largest diameter of OMA after 12 months of treatment with 2 mg of dienogest daily in which the largest proportional change was seen over the first six months of treatment. However, serum AMH concentration showed a slight and insignificant decline at the end of 12 months when compared with initial levels. Notably, endometriosis-related pain symptoms decreased significantly at both six and 12 months of treatment compared to baseline.

The optimal management for preserving ovarian reserve, reflecting the primordial follicle pool, is unclear among patients with OMA cysts. In a recent systematic review and meta-analysis, the authors reported that the presence of an ovarian OMA was associated with a decreased number of antral follicles (11). Although those findings might be attributed to the obstacles to clear visualization of antral follicles with US, Kitajima et al. (11) found that the follicular density in the ovary with OMA was significantly lower and the number of atretic early follicles were higher when compared with the contralateral unaffected ovary (12). These results suggest that there might be a genuine decrease in the number of antral follicles in women

with OMA, rather than a practical issue in the visualization. In the current analysis, based on a high inter-cycle variability of antral follicle count (13), and its inherent drawbacks, such as operator dependency, we preferred to follow the patients with AMH instead.

In the context of a comparison with non-endometriotic ovarian cysts, a systematic review and meta-analysis showed that the presence of an ovarian OMA was associated with a significant decrease in serum AMH levels when compared with otherwise healthy women (11). Furthermore, in a prospective cohort study by Kasapoglu et al. (13), it was noted that the serum AMH value decreased at the sixth month with the expectant observation of the patient with OMA (n=40), which was significantly higher than in an age-matched healthy control group (7.4%, n=40, p=0.01) (14). However, an observational cross-sectional study including 267 patients showed that serum AMH levels increased with OMA size in women without prior history of surgery (15). More recently, a follow-up study of 332 women with OMA, mainly size >6 cm, and regardless of age or bilaterality had significantly elevated preoperative AMH levels were significantly elevated, thus confirming these earlier findings (16). As high AMH concentrations in women with large ovarian OMAs have been reported in two different populations of women suffering from endometriosis by different teams, such an unexpected pattern might be explained by two hypotheses: 1) an increased leakage to the circulatory system due to increased local blood clearance boosted by an increase in ovarian blood flow associated with inflammation and neoangiogenesis in the nearby cortical tissue (15); and/or 2) expanded production of AMH from dysfunctional granulosa cells because of altered micro-environment because of increased expression of genes in the prostaglandin and corticosteroid pathways, in increased transformation of the cellular cytoskeleton, histone adjustments and DNA methylation at particular genes involved in steroidogenesis (17).

Dienogest is a fourth-generation progestogen and the only oral, disease-specific treatment for endometriosis. Given its excessive tolerability and efficacy, dienogest has become an essential choice for the treatment of endometriosis. Studies have shown that dienogest has high specificity for progesterone receptors; it exhibits antiandrogenic, antiproliferative, antiangiogenic and anti-inflammatory effects in endometriotic implants (18,19). Although dienogest has been reported to yield a significant reduction in OMA size/volume (20) its role on the dynamics of AMH is relatively less well known. According to the only study published to date, a reduction of 40% in diameter of OMA was observed in 32 patients without any change in AMH concentration when compared with baseline levels (21). As our study with a slightly larger sample size confirmed, the lack of any drop and even the presence of a plateau in AMH concentration after six months, one may suggest that dienogest may be useful to halt or at least slow-down the classical decrease in AMH concentration in the short term.

In theory, the observed improvement in the expected decline of AMH concentration might be related to decreased inflammation and angiogenesis in nearby cortical tissue or recovery of granulosa cell function due to an altered micro-environment after administration of dienogest. Further preclinical studies are needed to address the exact interaction between the endometriotic tissue lining the internal surface of OMAs and the closely associated tissues of the ovarian cortex.

Seven out of ten women diagnosed with endometriosis have abdominal pelvic pain, dysmenorrhea, or menorrhagia. Pelvic pain significantly affects the quality of life and has an important place in the treatment of endometriosis (22). Dienogest has demonstrated equal efficacy to GnRH analogues in the treatment of endometriosis and is efficient in alleviating endometriosis-related pain (23). Strowitzki et al. (23), in a double-blind placebo-controlled study, showed that dienogest was significantly more effective than placebo in reducing endometriosis-related pelvic pain over 12 weeks in 198 women (24). In their prospective cohort study with 37 patients, Kizilkaya et al. (25) demonstrated a 31% reduction in OMA size over a three-month follow-up period among individuals receiving dienogest 2 mg/day. Furthermore, there was a significant decrease in pain scores, including a 35.5% reduction in dysmenorrhea VAS score, a 37.5% reduction in dyspareunia VAS score, and a 38.5% reduction in chronic pelvic pain VAS score (25). In the current study and concordant with the literature, a significant reduction in pain scores was observed at the sixth and twelfth months of treatment compared with baseline VAS scores.

The lack of a control group limits the possibility of drawing firm conclusions about the efficacy and effectiveness of a particular treatment or intervention. However, as there is earlier evidence of the pattern of AMH in patients without any treatment (11), we believe that the results of AMH concentrations at certain time-points after commencement of dienogest is still useful. The second limitation might be the retrospective design of the study and its inherent drawback, but the paucity of data with respect to a follow up of 12-months makes the results of the study clinically informative.

Conclusion

In conclusion, daily administration of 2 mg of dienogest resulted in a significant decrease in the diameter of OMA after six months of treatment. Furthermore, there was a significant change in mean AMH concentrations after 12 months of treatment. This latter finding may be related to an

improvement in inflammation and angiogenesis in the nearby non-endometriotic cortical tissue.

Ethics Committee Approval: *The study was approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee (approval number: 2021/09-30, date: 20.04.2021).*

Informed Consent: *Informed consent was obtained from all patients participating in the study.*

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

Management of menopause in women with a history of endometriosis

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Abstract

Due to increasing life expectancy, women spend a significant part of their lives in menopause. Women with a history of endometriosis are more likely to become menopausal at an early age due to bilateral oophorectomy or repeated ovarian surgery. In addition, some medical therapies used for endometriosis, such as gonadotropin releasing hormone agonists or progestins reduce bone mineral density. Furthermore, women with endometriosis have a higher background risk of cardiovascular disorders and hypercholesterolemia. Hence, it is important to recommend the use of hormone replacement therapy (HRT) to these women when they become menopausal, at least until the age of natural menopause. Although based on limited data, there is a possibility of reactivation of symptoms of endometriosis or its lesions, and a theoretical possibility of malignant transformation, although this remains unproven. Therefore, women should be advised in the light of this information before starting HRT after the age of natural menopause and are asked to seek help if they experience symptoms that may indicate these changes. Estrogen only HRT should be avoided and combined HRT preparations should be recommended, even after a hysterectomy. (J Turk Ger Gynecol Assoc 2024; 25: 107-11)

Keywords: Endometriosis, menopause, HRT, postmenopausal endometriosis

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Introduction

Endometriosis is estimated to be present in 5-10% of women in the general population, while postmenopausal women form 2-5% of cases in the published series (1-5). As in reproductive age women, the correct prevalence of endometriosis in menopausal women is not clearly known due to some women being asymptomatic (6). Endometriosis is a hormone dependent condition; it is rare or absent before menarche, it commonly affects reproductive age women, its prevalence reaching a peak in the late reproductive years and it regresses after menopause (7,8). Although many women become asymptomatic after menopause, some will continue to have symptoms. Persistent/recurrent symptoms may be due to hormone replacement therapy (HRT) but some women are still symptomatic despite not being on HRT (9). It is postulated that extra-ovarian (conversion of androgens in the adipose tissue depending on body weight) or locally produced estrogens (due to increased aromatase activity in endometriotic tissue) continue to stimulate endometriotic lesions in symptomatic women (10-13).

In clinical practice, menopausal women may present either following natural menopause or following surgery to remove ovaries with or without removal of the uterus/endometriosis as part of their treatment for endometriosis. Endometriotic tissue may still be present in some menopausal women even after prior surgical treatment, as there may be residual or recurrent lesions of endometriosis in a significant proportion.

Adverse health outcomes of early surgical menopause, such as dementia, cardiovascular disease and osteoporosis, are

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well known and this applies to women with a history of endometriosis (14). These women may even be at higher risk due to the possible use of medical therapies that may have caused reduced bone mineral density (BMD), such as gonadotrophin releasing hormone (GnRH) analogues or progestins. In addition, women with endometriosis are known to have a higher background risk for hypercholesterolemia and cardiovascular diseases, or conditions predisposing to cardiovascular disease such as hypertension (15,16). Therefore, use of HRT becomes an issue of discussion during consultations with these women (15,16).

In this article we will give a practical overview of management of postmenopausal endometriotic symptoms, use of HRT in postmenopausal women with a history of endometriosis and future risk of malignancy.

Management of symptomatic postmenopausal women with endometriosis

There are few data in the literature on treatment modalities for symptomatic post-menopausal endometriosis. Pelvic pain tends to be the most common presenting symptom, mostly caused by endometriotic lesions, as in reproductive age women (13). Others may present with a pelvic mass or some form of bleeding, such as vaginal bleeding, hematuria, rectal bleeding, and hemoptysis (9). Since the risk of malignant disease is naturally higher in women with endometriosis than in other groups, a careful examination of the genital, gastrointestinal and urinary tracts with appropriate imaging should be performed, depending on the nature of the symptom(s) (3,17).

If the symptoms are triggered by initiation of postmenopausal HRT, consideration can be given to discontinuation of HRT, following discussion with the woman. This may be more acceptable if the woman has become menopausal naturally. However, in early menopause, particularly following surgical menopause, concern over the detrimental impact of hypoestrogenism may make this approach less viable (10). Other approaches include reducing the dose of estrogen, switching from sequential to continuous combined HRT and changing the type of progesterone.

Medical treatment options for symptomatic endometriosis are limited in postmenopausal women. Limited data published in the literature suggest aromatase inhibitors (AI), including anastrazole, letrozole or exemestane, can be administered orally at doses of 1-5 mg/day, especially when surgery is not feasible. The main mechanism of action of AI is the inhibition of cytochrome P450, which catalyzes the conversion of androgens to estrogens. They not only inhibit estrogen production in the ovaries, adrenal glands, brain, and peripheral adipose tissue but also regulate local estrogen formation in endometriotic lesions as well (11). These drugs have been reported to be effective in treating postmenopausal recurrence, reducing mass and decreasing pressure, as well as having a good safety record in the development of postmenopausal breast cancer (12). However, AI increase the possibility of osteoporosis in the long term (18). Besides, BMD may have already diminished due to prior use of GnRH agonists or progestins in patients with endometriosis (19). Additional bone loss due to the menopausal process requires special attention due to the possible low background BMD in these patients (20). It should be remembered that BMD decreases significantly after treatment with AI, even with concomitant use of calcium and vitamin D (21). Hot flashes, vaginal dryness, and arthralgic symptoms are the other possible side effects (21).

Surgery remains a viable option for symptomatic postmenopausal women, especially if there are visible endometriotic lesions on imaging, particularly when new ovarian cysts develop. The presence of suspicious appearances within endometriotic lesions, either within or outside the ovaries in women after the age of natural menopause should prompt appropriate investigations and treatment following local guidelines. Even in the absence of any suspicious lesions, surgery would usually involve removal of the ovaries, uterus and endometriotic lesions, if surgical treatment is chosen (Figure 1).

Use of HRT in women with a history of endometriosis

HRT is effective in relieving menopausal symptoms, but its use in postmenopausal endometriosis patients may lead to reactivation of symptoms or endometriotic lesions and malignant transformation (22). Currently, there is limited published information on the efficacy of HRT in relieving menopausal symptoms, specifically in women with a history of endometriosis (13). Most published data come from studies which report on the efficacy of HRT following surgical menopause, hence there is no data on the use of HRT in women with endometriosis who have reached menopause naturally (13). Patients who undergo surgical menopause for endometriosis at a younger age report sudden onset of more severe menopausal symptoms (23).

Considering the aforementioned health risks in women with a history of endometriosis who become menopausal earlier than the natural age of menopause, HRT is strongly recommended, at least until the age of natural menopause (13,24). It has been reported that 40% of endometriosis patients do not take HRT after hysterectomy and oophorectomy, including those who enter surgical menopause prematurely (25). Therefore, it is suggested that consideration could also be given to ovarian preservation in hysterectomy for endometriosis (25).

Due to the risk of recurrence of endometriosis or its symptoms, and the theoretical risk of malignant transformation, use of

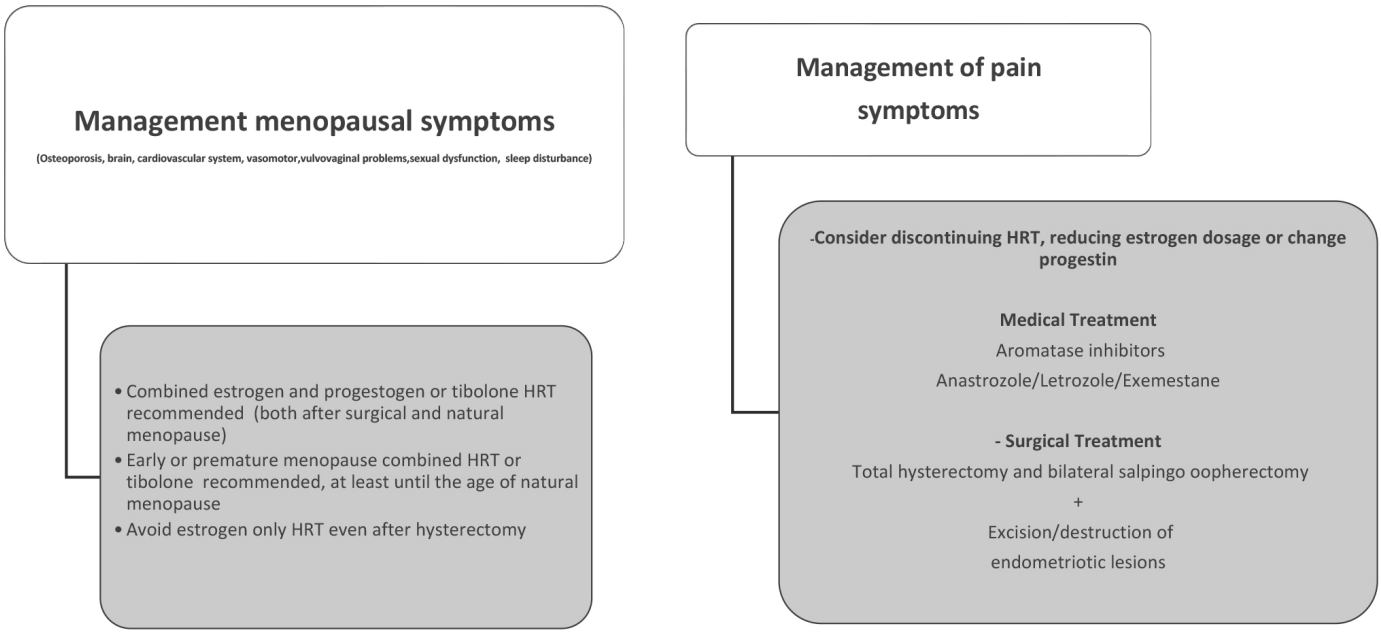

Figure 1. Management of postmenopausal endometriosis

combined HRT with estrogen and progesterone or tibolone has been recommended, even after hysterectomy, in international guidelines such as the European Society of Human Reproduction and Embryology and European Menopause and Andropause Society for women with a history of endometriosis (13,24). A potential disadvantage of using progesterone in all women with a history of endometriosis is a slight increase in risk of breast cancer, compared to estrogen only HRT (26).

A survey conducted among a total of 216 physicians in the United Kingdom revealed that only two-thirds of the gynecologists/menopausal physicians prescribe combined HRT, 11.1% use tibolone, 13.0% only estrogen HRT and 7.8% prescribe variable HRT (27). The underlying reason for this was that some physicians stated they would not prescribe HRT because there was insufficient evidence to support this, while others argued that HRT was only necessary for severe symptoms, especially if the lesions had not been effectively removed. In addition, some doctors were concerned about progestogen-associated increased risk of breast cancer (28).

Matorras et al. (29) compared women who received HRT (n=115) following bilateral salpingo-oophorectomy (BSO) ± hysterectomy with a control group (n=57) who did not receive HRT following surgery. In the group of patients who started treatment four weeks after BSO surgery, 3.5% had recurrent symptoms after approximately four years, whereas there were no recurrences in the group who did not receive HRT. The risk of recurrence was higher, especially in cases in which hysterectomy was not performed, or a subtotal hysterectomy was performed (as opposed to total hysterectomy) and in those with endometriotic lesion >3 cm. These differences were not statistically different but the numbers were too small to reach statistical significance (29). Another non-randomised retrospective study from Thailand showed recurrence of endometriosis symptoms in 6% of 50 (n=3) women who used estrogen only HRT compared to those who did not use HRT (n=17) or used combined HRT (n=40) following surgical menopause (30).

Based on this limited information there is overall agreement that HRT can be used in women with a history of endometriosis for the treatment of menopausal symptoms and to protect bone health in the long term. Combined HRT is recommended and use of estrogen only HRT should be avoided (13,31).

HRT in women with a history of menopause and risk of malignant transformation

Malignant transformation whilst using HRT is uncommon and has only been published in case reports. Some studies have shown that the prevalence of ovarian cancer in women with endometriosis is higher than that of sporadic ovarian cancer in the general population (32). A systematic review and meta-analysis of published studies showed that, whilst there is no overall increase in risk of cancer in women with a history of endometriosis, the lifetime risk of ovarian cancer increased from 1.3% in the general population to 2.5%, breast cancer from 12.8% to 13.4% and thyroid cancer from 1.3% to 1.8%, whereas the risk of colorectal cancer did not change and the risk of cervical cancer was lower (33). In another systematic review, Gemmel et al. (22) found malignant transformation

in 25 patients between the ages of 38 and 75 years. The most common complaints in these patients were vaginal bleeding, pain, a mass in the pelvis, weight loss, constipation and flank pain. Histologically, the most common malignancies were endometrioid adenocarcinoma and the other histological types included adenosarcoma, clear cell cancer, Mullerian carcinosarcoma and endometrial stromal sarcoma. Of these, 76% had received unopposed estrogen therapy and three of these 25 women died from cancer.

The impact of HRT on malignant transformation of endometriosis remains uncertain. A recent study from South Korea examined 20,608 postmenopausal women with de novo endometriosis or a history of endometriosis and compared the impact of HRT on the risk of ovarian cancer. These authors showed that HRT did not increase the risk of ovarian cancer (34).

Conclusion

Women with a history of endometriosis are more likely to undergo repeated surgery with decreasing ovarian reserve and early menopause due to removal of ovaries. In addition, some medical therapies used for endometriosis, such as GnRH agonists or progestins reduce BMD. Furthermore, women with endometriosis have a higher risk of cardiovascular disorders and hypercholesterolemia. Hence, it is important to recommend use of HRT to these women when they become menopausal at an early age, at least until the age of natural menopause. Although based on limited data, there is a possibility of reactivation of symptoms of endometriosis or its lesions, and a theoretical possibility of malignant transformation, although this remains unproven. Women should be advised to consider these before starting HRT and are asked to seek help if they experience symptoms, which may indicate these changes. Estrogen only HRT should be avoided and combined HRT preparations should be recommended even after a hysterectomy.

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Is sentinel lymph node identification warranted as a routine approach for patients with vulvar verrucous cancer?

To the Editor,

With a great deal of interest, we read the article entitled "Indocyanine green fluorescence imaging: an effective method to find inguinal sentinel lymph node in a case of vulvar carcinoma" by Wunster et al. (1). The authors present a case report of sentinel lymph node (SLN) identification in a patient with vulvar cancer using the combination of near-infrared range/indocyanine green (ICG) and technetium-99m (Tc-99m) techniques. The patient had stage Ia1 squamous verrucous cancer.

We would like to highlight a recently published study by Guijarro-Campillo et al. (2), comparing the ICG technique to the standard Tc-99m technique (dual-modality method). The study revealed an overall SLN detection rate of 85.3% for Tc-99m and 82.7% for ICG. In addition, the sensitivity and positive predictive value for ICG compared to Tc-99m were 91.08% and 94.8%, respectively. We congratulate the team of Wunster et al. (1) for presenting their video article. However, we would also like to draw attention to the fact that vulvar verrucous carcinoma is a rare variant of squamous cell cancer, with a controversial surgical approach.

In a recent literature review by Zhang et al. (3), the authors demonstrated that although preoperative imaging could suggest suspicious inguinal lymph node metastasis, the role of lymph node assessment is controversial. Specifically, this literature review found that inguinal lymph node metastasis rarely occurs and was not identified in any of the 50 verrucous cancer patients in the literature, regardless of the approach (systematic inguinal lymphadenectomy or SLN protocol).

Once again, we congratulate the authors for their innovative technique.

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Author's Response

Dear colleague,

Thanks for having shared the interesting review about verrucous vulvar cancer.

In spite off the rarity of groin lymph node metastasis in the verrucous variant of squamous cell carcinoma, we decided to conform to ESGO vulvar guidelines 2023 in the treatment of our patient.

ESGO guidelines don't differ about hystological subtype for the surgical treatment and SLN procedure of the vulvar cancer.

ESGO guidelines also support, for SLN procedure, combination detection techniques as blue dye and Tc-99m nanocolloid, and promising association of ICG and isotope, like in our video article.

Yours sincerely,

Silvia Von Wunster[1], Paola Algeri[2], Laura Colonna[1], Maria Chiara Slompo[1], Silvia Bergamelli[1], Laura Imbruglia[1], Maria Enrica Pina[3]

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Further reflections after the second surgery step in a case of uterine malformation diagnosed in the shock room

To the Editor,

Recently we published a paper in the Journal of Ultrasound, titled "A uterine malformation diagnosed in the shock room: a case report which helps to identify how to avoid a potentially preventable life-threatening event" (1), describing a uterine rupture at 15.6 gestational weeks, due to a unicornuated uterus with a communicant residual right horn not diagnosed before pregnancy. This case highlighted the importance of the ability to diagnose uterine malformations at the first gynaecological evaluation, using a combination of abdominal-vaginal 2D-ultrasound, (2) as early detection is essential in reducing the risk of life-threatening events in case of pregnancy.

We want to share the subsequent management of this patient in order to demonstrate how correct management before pregnancy allowed for a reduction in surgical complications. This is good for the patient but challenging for the surgeons.

A year later this patient underwent surgery because she wanted further pregnancies. In this case in unicornuate uterus, the uterine horn should be removed to reduce its association with worsening obstetric outcomes (3,4). The initial approach was laparoscopic. Unfortunately, the patient had several abdominal adhesions and an intestinal injury was caused during the attempt to access. After a subsequent conversion to laparotomy, the rudimental horn was removed and an ileal resection was required for surgical complications, although her postoperative course was uneventful with discharge on the fifth day.

This uterine rupture was an emergency, and the surgeons were faced with an unexpected uterine malformation in an unstable patient. However, we believe that the possibility to remove the uterine horn during any emergency laparotomy for uterine rupture, should always be considered after patient stabilization.

To allow adequate correction the surgeons should be trained to distinguish a unicornuate uterus, in which the removal of the horn could be suggested, from a bicornuate uterus, in which the approach should be conservative. Moreover, although a second surgery would potentially reduce the risk of misdiagnosis, performing a single procedure has several advantages. In particular, it abolishes the waiting time for a second pregnancy, and also reduces the risk of organ injury due to abdominal adhesions.

Furthermore, if a second surgery is required, we recommend a left sub-costal Palmer's access and/or an access under optical guidance in order to reduce the risk of organ injury.

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CONGRESS CALENDER

INTERNATIONAL MEETINGS

(for detailed International Meeting please go website: https://www.emedevents.com/obstetrics-and-gynecology)

June 10-14, 2024	The Society of Obstetricians and Gynecologists of Canada Annual Clinical Scientific Conference, Edmonton, Canada
June 19-22, 2024	International Urogynecological Association (IUGA) 49th Annual Meeting, Singapore
July 07-10, 2024	European Society of Human Reproduction and Embryology (ESHRE) 40th Annual Meeting, Amsterdam, Netherlands
September 11-13, 2024	XXIX. European Congress of Perinatal Medicine, Vienna, Austria
October 06-09, 2024	34th ISUOG World Congess, Dubai, UAE
October 16-18, 2024	International Gynecologic Cancer Society (IGCS) 2024 Meeting, Dublin, Ireland
October 19-23, 2024	American Society for Reproductive Medicine (ASRM) 80th Annual Meeting, Denver, Colorado, United States
October 19-22, 2024	19th World Congress on Menopause, Melbourne, Australia
October 27-30, 2024	ESGE 33rd Annual Congress, Marseille, France
November 17-20, 2024	The 53rd American Association of Gynecologic Laparoscopists (AAGL) Global Congress on Minimally Invasive Gynecologic Surgery (MIGS), New Orleans, Lousiana, United States
November 21-23, 2024	The 32nd World Congress on Controversies in Obstetrics Gynecology & Infertility (COGI), Lisbon, Portugal
April 23-27, 2025	**XV. Turkish-German Gynecology Congress, Antalya, Turkey**

CONGRESS CALENDER

NATIONAL MEETINGS

(for detailed International Meeting please go website: https://www.kongreuzmani.com/2024)

May 31-June 1, 2024	TAJEV Obstetrik ve Jinekolojide Güncel Yaklaşımlar Sempozyumu, İstanbul, Türkiye
September 06-08, 2024	3. Uluslararası Pelvik Taban ve Kozmetik Jinekoloji Kongresi, İstanbul, Türkiye
September 18-22, 2024	7. Minimal İnvaziv Jinekolojik Cerrahi Kongresi, İstanbul, Türkiye
October 02-06, 2024	6. Jinekoloji ve Obstetrikte Tartışmalı Konular Kongresi, Antalya, Türkiye
November 14-17, 2024	12. Üreme Sağlığı ve İnfertilite Kongresi, Antalya, Türkiye