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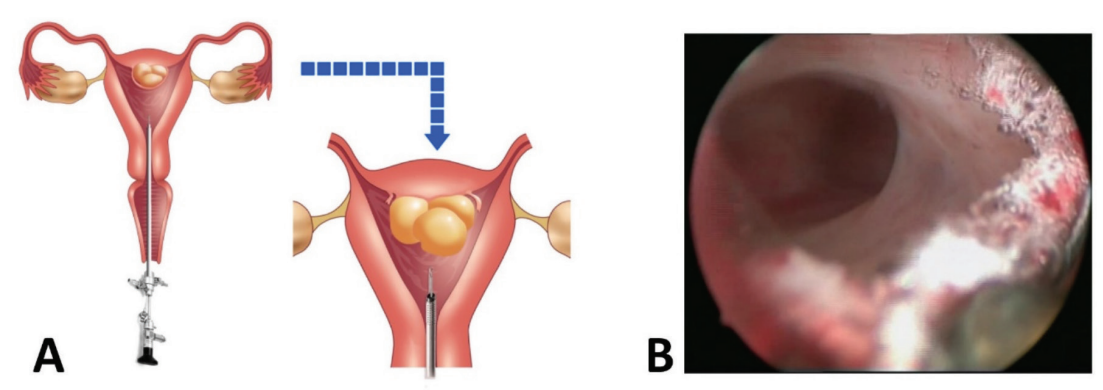

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Cover Picture: Tahermanesh et al. The Blooming phenomenon

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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.

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

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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/),

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

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

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

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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.

Discussion

State the importance and significance of your findings but do not repeat the details given in the Results section. Limit your opinions to those strictly indicated by the facts in your report. Compare your finding with those of others. Provide information on the limitations and strenghts of the study. No new data are to be presented in this section.

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

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Book chapter;

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Book;

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

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

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Contents

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Editorial

Dear Colleagues,

It is my great pleasure to introduce the first issue of the "Journal of the Turkish-German Gynecological Association (J Turk Ger Gynecol Assoc)" in the publishing year of 2025. This issue is consisted of seven articles, and two reviews that we hope you will read with interest. Also you may have the oppurtunity to read the quiz. Here we share some of our favorite articles that were published in this issue of the journal.

The symptoms of genitourinary syndrome of menopause (GSM) include urinary symptoms in addition to genital (dryness, burning, and irritation) and sexual (lack of lubrication, discomfort or pain) symptoms. Relieving symptoms is the main goal of GSM treatment. Non-hormonal vaginal lubricants for use during sexual activity, long-acting vaginal moisturizers, systemic hormonal therapies, low-dose vaginal estrogen therapies (such as vaginal creams, intravaginal tablets, or intravaginal rings), and platelet concentrates are among the current treatment options. The liquid form of platelet-rich fibrin (i-PRF) contains more white blood cells, platelets, and a higher level of cellular migration than PRF.

You will have the opportunity to read an article investigating the efficacy of i-PRF for GSM.

Pituitary adenomas are relatively common, occurring in 80-100 cases per 100,000 people, of which 15-30% are non-functioning pituitary adenomas (NFPAs). Managing NFPA during pregnancy can be challenging and requires interdisciplinary care. There isn't much research examining the relationship between NFPAs and pregnancy. You will also have the opportunity to read an article looking into how NFPAs affect pregnancy and associated illnesses with an emphasis on issues such symptoms brought on by adenoma size during pregnancy, delivery techniques, unfavorable pregnancy outcomes, and lactation duration.

You will also have the opportunity to read a review focusing on restorative treatment protocols that dentists would apply to patients in the puerperal period and the maintenance of these treatments.

I would also like to invite you to join us for our prestigious 15th Turkish-German Gynecology Congress which will be held in Antalya between April 23-27 of 2025. As of before, our congress will be held to the highest scientific standards with a rich scientific program and pre-congress courses. At this year's congress we will be having lectures with the world's most reputable speakers; Prof. Gunter Noe (vNotes and Prolapse surgery; a critical discussion), Prof. Ceanea Nezhat (Revisiting microsurgical principles), Prof. Stefan Verlohren (Preeclampsia screening and prediction), Prof. Ertan Sarıdoğan (What is the significance of T-shape uterus in reproduction?).

Dear Researchers,

The XV. Turkish German Gynecology Congress will reward the best 3 abstracts. The purpose of this reward is to show our colleagues our appreciation for their productivity and also motivate our young colleagues for the forthcoming years. Also the best video presentation which will be elected by the Scientific Committee will receive a 20,000 TL "Dr. Aysun - Cihat Ünlü Special Reward." Also there will be the Turkish-German Gynecological Education and Research Foundation reward of 30,000 TL.

Dear Esteemed Readers, Authors and Reviewers,

As one of the chief editors of JTGGA, Prof. Dr. Peter Mallmann has made significant contributions to our journal over the years. As of 2024, he is retiring. Throughout his tenure, he has not only enhanced the scientific quality of our journal but also played a pivotal role in strengthening international academic collaboration and promoting high-quality publications in our field. With his scientific rigor, academic discipline, and unwavering support for young researchers, he has brought invaluable vision to JTGGA. We extend our deepest gratitude to Prof. Dr. Mallmann for his invaluable contributions and wish him health, happiness, and success in his retirement.

Please do not forget to mark the congress on your calendars in order to not to miss this scientific festival. 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

Usefulness of delayed primary closure in unplanned caesarean section to reduce surgical site infection in a resource-poor high population country: a randomised controlled trial

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Abstract

Objective: Surgical site infection (SSI) is a common complication, especially following emergency caesarean section (CS) leading to maternal morbidity and prolonged hospital stay. Results are conflicting regarding the ideal method of skin closure after abdominal surgery in clean contaminated and contaminated wound. To compare the outcome of wound health between primary and delayed primary closure (DPC) of skin incision in emergency CS.

Material and Methods: A total of 70 pregnant women undergoing emergency caesarean deliveries with a history of membrane rupture were randomized into group A (n=40) and group B (n=30). In group A monofilament sutures were placed in skin incision but the wound was left open for daily dressing with normal saline. It was closed by tying the monofilament sutures on fifth day and stitches were removed on seventh day. In group B skin was apposed by a routine primary closure procedure.

Results: No patient in group A required secondary wound closure following SSI ($p<0.001$) and duration of hospital stay was also significantly reduced ($p<0.05$).

Conclusion: This trial demonstrated that DPC is effective in reduction of requirement of secondary stitches due to SSI in emergency CS. (J Turk Ger Gynecol Assoc. 2025; 26: 1-6)

Keywords: Caesarean section, surgical site infection, primary closure, delayed primary closure, membrane rupture

Received: 24 July, 2024 **Accepted:** 19 November, 2024 **Publication Date:** 12 March, 2025

Introduction

Worldwide, the current rate of caesarean section (CS) is around 21% and it has been steadily increasing over the last three decades. By 2030, the global CS rate is projected to reach nearly 30%, making it a very common mode of delivery, particularly in Latin America and Eastern and Western Asia (1). Surgical site infections (SSI) are the second most common type of infection following caesarean deliveries, surpassed only by urinary tract infections (2). Though SSI rarely becomes life-

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threatening, it is associated with significant morbidity, often leading to prolonged hospital stays and increased economic burden on the healthcare system. The incidence of SSI is much higher (23.2%) in resource-poor countries despite adjustment for related factors including diseases, operative procedures, hospitals, and safety (3). The overuse of antibiotics in the postoperative period further exacerbates antimicrobial resistance, thereby increasing the risk of SSI (4).

Caesarean deliveries performed in emergency situations with ruptured amniotic membranes are considered clean-contaminated procedures, and are associated with a 10-20% rate of wound disruptions (5-7). While antibiotic prophylaxis is recommended for clean-contaminated wounds, it may not fully prevent the complications arising from intraoperative contamination (8).

Wound dehiscence, or the separation of the incision, complicates 2-7% of CS. It often occurs due to the formation of a wound hematoma or seroma, which serves as a nidus for infection (9,10). Studies have shown that delayed primary closure (DPC) may effectively reduce wound infection rates compared to primary closure (PC) of skin margins. DPC offers advantages over PC, including lower infection rates and improved wound strength at 20 days (11).

The value of DPC in managing contamination has long been recognized by military surgeons. There are fundamental physiological concepts of wound healing that support the mechanism of DPC. In PC, epithelialization produces an airtight seal within 24 hours, allowing bacteria to become trapped in the subcutaneous tissue. In areas with poor vascularization, blood clots and wound debris, this creates an ideal environment for bacterial growth in contaminated wounds. In addition, collagen tissue is not produced until the 4^{th} to 5^{th} postoperative day. In contrast, DPC involves both primary and secondary intention healing, allowing for accelerated tensile strength due to more effective cross-linking between collagen subunits (12). DPC is proven to be highly effective in complex, contaminated abdominal wall repairs, leading to reduced wound complications and faster healing times (13). In this randomized trial, our aim was to compare the outcomes of wound healing between DPC and PC following emergency CS.

Material and Methods

An open-label randomized controlled trial was conducted at a tertiary care centre in Kolkata, India. Pregnant women undergoing emergency CS were enrolled between March and June 2021. The study was initiated after receiving approval from the Calcutta National Medical College Institutional Ethics Committee (approval number: 91, date: 04.09.2020), following the principles of Helsinki Declaration of 1975, as amended in 2013, and was registered on ClinicalTrials.gov with Identifier: NCT04587960. Written informed consent was obtained from each eligible participant. During the study period, only those participants with ruptured membranes were included. The wound was classified as either clean-contaminated (if membrane rupture was less than 12 hours) or contaminated (if more than 12 hours), as previously described (14,15). Women with ruptured membranes who were undergoing CSs were counselled about the two different types of skin closure techniques and were screened for eligibility. Women with intact membranes, those requiring an incision other than a Pfannenstiel incision, or those exhibiting features of chorioamnionitis were excluded from the study. In addition, women who were on immunosuppressive medications, had a history of chemotherapy, or had conditions that could interfere with wound healing, such as diabetes mellitus, tuberculosis, or collagen vascular disease, were also excluded. Once the decision for emergency CS was made, participants were randomized through a computer generated number sequence into group A (study group) and group B (control group). All participants received a 1-gram ampicillin injection prophylactically within thirty minutes of the abdominal incision. In group A, after the rectus sheath was closed with 1-0 polyglactin at the end of the procedure, the skin and subcutaneous tissue were left open. Stitches were placed with 1-0 monofilament, but knots were not tightened. From the second day onwards, wound dressing was performed using normal saline after cleaning the skin with 5% povidone-iodine solution for three consecutive days. On the fifth day, the stitches were tightened under local anesthesia to approximate the skin margins, and they were removed on the seventh day. In group B, the skin incision margins were approximated using routine PC, with 1-0 monofilament, and the stitches were removed on the sixth day after the CS. For any abnormal discharge from the wounds, swabs were taken for bacterial culture and sensitivity testing. In cases of wound dehiscence, secondary closure was performed once adequate granulation tissue had developed after wound dressing with normal saline and antibiotic ointment. Demographic information, indications for CS, and other variables such as age, parity, body mass index (BMI), previous surgical scars, medical comorbidities, and whether labor was induced or augmented were recorded. Surgery-related data included the duration of the procedure, preoperative and postoperative hemoglobin and hematocrit levels, as well as the length of hospital stay in days.

Statistical analysis

In calculating the sample size, we assumed the need for secondary sutures in 17% of participants in group A and 32% in

group B, based on a previous meta-analysis. Based on a superiority margin of -10%, assuming 80% statistical power and an alpha level of 0.05; a sample size of 36 in each group was needed. For data analysis, continuous data are represented as mean ± standard deviation for normally distributed variables, and as median (interquartile range) for non-normally distributed variables. Categorical data are represented as percentage (frequency). Mean comparisons were conducted using the Mann-Whitney U test. Proportions were compared using the chi-squared test or Fisher's exact test, where applicable. For variables with multiple levels of ordered categories, unadjusted p values were reported with Bonferroni correction to control for the family-wise error rate. In the cross-tabulation of the need for secondary sutures against groups (A or B), quasi-complete separation of data was observed (no secondary sutures were needed in group A). Multivariate modeling with logistic regression, with the former as the dependent variable and the latter as one of the independent variables, were corrected using the Bias-Reduced Logistic Regression (firth regression). All statistical analyses were performed using SPSS, version 20 (IBM INC., Armonk, NY, USA).

Results

Overall, 70 patients were included in the study with a mean age of 25.1±4.46 years, and 45.7% (32/70) were nulliparous. Patients were randomized into two groups: DPC (group A, n=40) and PC (group B, n=30) (Figure 1). The demographic and clinical details of both groups are provided in Table 1. The groups were comparable in terms of the presented parameters. The duration of the operation (OT) did not differ significantly between the groups, with group A having an average duration of 58.5±15.8 minutes and group B averaging 58.7±18.5 minutes (p=0.96).

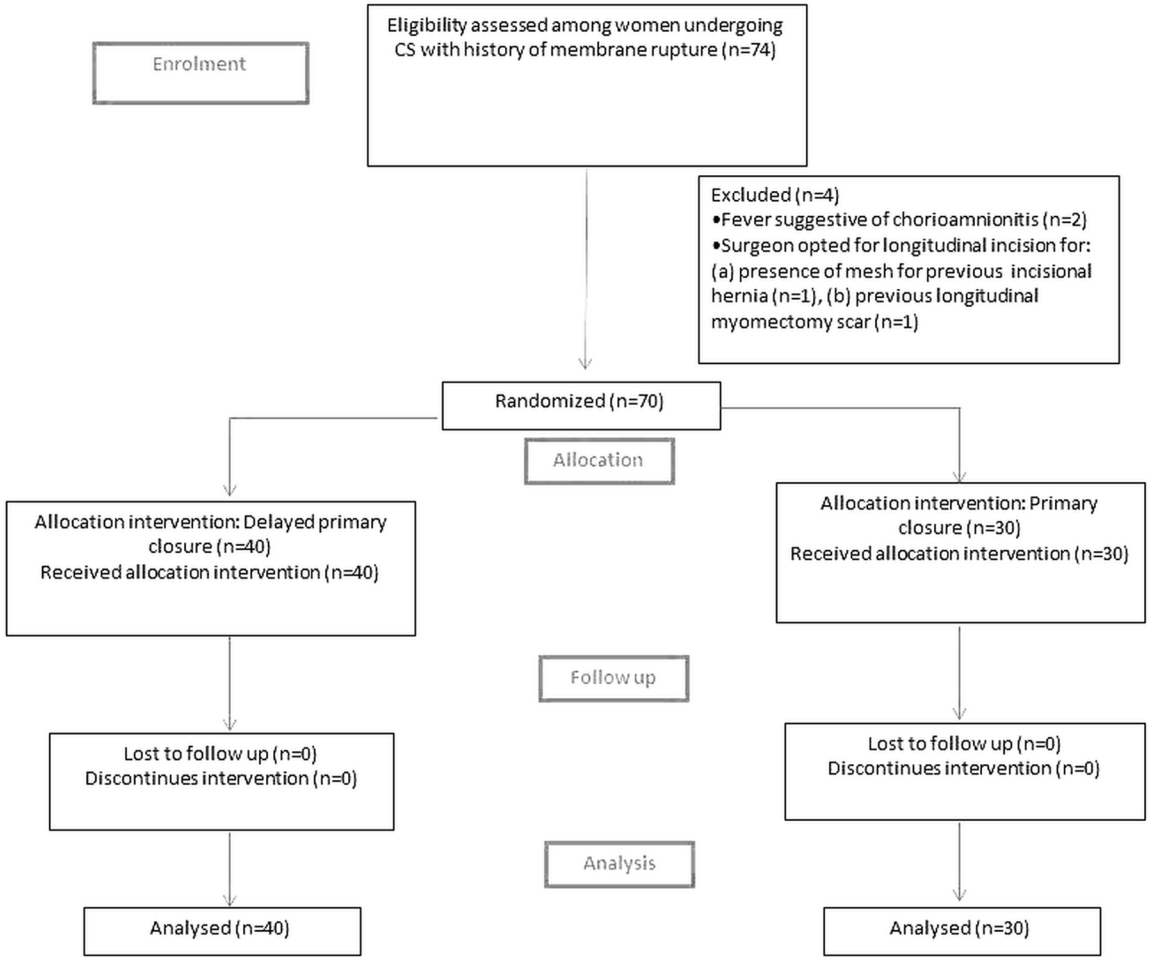

Figure 1. CONSORT flow diagram
CS: Caesarean section

The need for secondary sutures was absent in group A but was required in one-third of the patients in group B (Table 2) and this was significant (p<0.0001). Other secondary outcome measures are also given in Table 2. The duration of hospital stay was significantly shorter for patients undergoing DPC (7.6±3.4 vs. 5.6±0.5, p=0.003).

Prediction of secondary suture requirement

Univariate and multivariate regression results (Table 3) showed only one significant predictor for the need for secondary sutures in pooled data, the OT [odds ratio (OR): 1.06, 95% confidence interval (CI): 1.01-1.11, p=0.029].

Table 1. Baseline demographic and clinical information

Parameters		Primary closure group, (n=30)	Delayed primary closure group, (n=40)
	Age in years	24.6 (3.9)	25.6 (4.9)
	BMI in kg/m^2	21.3 (1.8)	22.8 (3.5)
Indications for CS	Post CS in labor	4 (13.3%)	10 (25%)
	Nullipara with medical complications	5 (16.6%)	4 (10%)
	Induction failure/non-progress of labor	5 (16.6%)	4 (10%)
	Post CS with medical complications	5 (16.6%)	6 (15%)
	Obstructed labor	3 (10%)	3 (7.5%)
	Elderly primigravida	1 (3.3%)	2 (5%)
	Placenta previa	2 (6.67%)	1 (2.5%)
	Fetal distress	3 (10%)	5 (12.5%)
	Breech presentation	2 (6.67%)	5 (12.5%)
	Presence of abdominal scar other than CS	9 (33.3%)	16 (25%)
	Presence of previous unhealthy scar	2 (6.67%)	5 (12.5%)
Parity	Nullipara	15 (50%)	17 (42.5%)
	Parity = 1	13 (43.3%)	19 (47.5%)
	Parity = 2	2 (16.67%)	3 (7.5%)
	Parity = 3	0	1 (2.5%)
	OT duration in minutes	58.5 (15.8)	58.7 (18.5)

BMI: Body mass index, CS: Caesarean section, OT: Operation

Table 2. Outcome measures

Parameters	Primary closure group, (n=30)	Delayed primary closure group, (n=40)	p
Secondary suture rate	9 (33.33%)	0	0.0001
Post OT haemoglobin level (gm/dL)	10.6±1.3	10.1±1.6	0.26
Duration of hospital stay in days	7.6±3.4	5.6±0.5	0.003

OT: Operation

Table 3. Prediction of need for secondary suture

	Univariate			Multivariate		
Variable	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age	0.99	0.85-1.16	0.98	NA		
OT duration	1.06	1.01-1.12	0.0009	1.06	1.01-1.11	0.029
BMI	0.88	0.68-1.14	0.8	NA		
Parity >0	3.38	0.65-17.63	0.15	NA		
Post OT hemoglobin	0.68	0.43-1.07	0.09	0.82	0.1-1.31	0.41

OR: Odds ratio, CI: Confidence interval, BMI: Body mass index, OT: Operation

Discussion

The National Nosocomial Infections Surveillance System of the Centers for Disease Control and Prevention risk adjustment index to stratify the risk of SSI involves three major factors: the patient's health status before surgery; the type of wound reflecting degree of contamination; and the duration of the OT. As the risk index score increases, so does the infection rate. However, this relationship has not been firmly established for SSIs after CS (16). An obstetric-specific risk factor is the duration of membrane rupture prior to caesarean delivery. Once the membrane rupture, the amniotic fluid is no longer sterile and can act as a medium for bacteria to contaminate uterine and skin incisions, thereby increasing the risk of wound infection (17,18). In the present study, all participants had a history of membrane rupture, with their wounds classified as either clean-contaminated or contaminated when the duration of membrane rupture exceeded 12 hours. Tran et al. (19) demonstrated that CSs lasting more than one hour were associated with a 2.4-fold increased risk of wound infection in univariate analysis, although they did not find its independent predictive value. In contrast, the present study found that both univariate and multivariate analyses identified the duration of the surgical procedure as a significant predictor of SSI requiring secondary suturing (OR: 1.06, 95% CI: 1.01-1.11, p=0.029). The risk of post-operative infection is proportional to the volume of blood loss during caesarean deliveries (20,21). A high volume of blood loss is associated with poor control of bleeding, prolonged retraction and use of more sutures, which can promote more contamination and reduce the local resistance mechanisms (19). In our study, we attempted to assess operative blood loss by recording pre- and post-operative haemoglobin levels. However, we did not find any causal relation between the post-operative decrease in haemoglobin values and the occurrence of wound infections requiring secondary suturing. One-third of participants required secondary stitches due to SSI when skin incisions were closed using PC (p=0.0001). This morbidity also significantly prolonged hospital stay (p=0.003). Therefore, DPC of skin incisions after caesarean deliveries appeared to play an important role in reducing SSIs, preventing further surgical interventions, and minimizing other related morbidities. A significant bacterial presence can delay wound healing after PC by directly "stealing" oxygen or increasing oxygen demand due to phagocytosis of bacteria. This leads to poor oxygen tension, which can compromise collagen synthesis, or the release of collagenase by bacteria or granulocytes may further inhibit collagen production (22). In addition, wound healing may be delayed due to inadequate blood supply in conjunction with infection (23). DPC, unlike delayed wound healing, is performed as a therapeutic intervention. Several animal studies have demonstrated that DPC results in superior mechanical strength, attributed to significantly higher perfusion, increased partial pressure of oxygen, and enhanced collagen synthesis and remodelling activity (24-26). Furthermore, in a propensity matched study, negative pressure wound therapy-assisted DPC was shown to have excellent effects on wound healing (13). Two retrospective studies of DPC have shown mixed results, while a meta-analysis of seven randomized controlled trials in the surgical literature demonstrated 0.50 relative risk reduction with DPC. One case report involving an obese parturient with a BMI of 61 kg/m^2 who underwent caesarean delivery due to failed induction of labor reported a favorable outcome with no complications (15). A recent review article also highlighted the beneficial effects of DPC in patients with comorbidities that might impair wound healing. However, it is important to note that although all studies included in the review were comparative, a significant portion were not randomized controlled trials, underscoring the need for further research to confirm these findings (27). Given this context, we undertook this clinical trial to strengthen the evidence supporting our conclusions. In the present study, we found that DPC was a safe and highly effective method for managing clean-contaminated or contaminated wounds after caesarean deliveries.

Study Limitations

The major limitation of this study was the small sample size. Due to the limited data available from a small number of studies, large-scale clinical trials are needed to more comprehensively evaluate the role of DPC in preventing SSIs, reducing prolonged hospital stays, and minimizing other morbidities following obstetric surgeries.

Conclusion

DPC of clean-contaminated skin incisions in CSs with prolonged membrane rupture may be a suitable option for preventing SSIs. This may be particularly true in high-population settings where procedure-related conditions may not always be optimal.

Ethics

Ethics Committee Approval: *The study protocol received approval from the Calcuttaa National Medical College Instituitional Ethics Committee (approval number: 91, date: 04.09.2020).*

Informed Consent: *Written informed consent was obtained from each eligible participant.*

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Footnotes

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Evaluation of *TNP1* and *PRM1* gene expression in male infertility patients with low or high sperm DNA fragmentation

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Abstract

Objective: The transition nuclear protein 1 (*TNP1*) gene is a member of the TNP family and is abundantly expressed during spermatogenesis. Protamine 1 (*PRM1*), another sperm nuclear protein, is abundant in many species. The present study aimed to evaluate transition nuclear protein 1 (*TNP1*) and protamine 1 (*PRM1*) gene expression in infertile male patients with low and high sperm DNA fragmentation (SDF).

Material and Methods: Semen samples (n=100) were obtained from male participants undertaking treatment with intracytoplasmic sperm injection. The expression levels of *TNP1* and *PRM1* were measured using real-time quantitative polymerase chain reaction. The data were compared with statistical tests, (independent samples T- or Mann-Whitney U) as appropriate. A $p<0.05$ was considered significant.

Results: Patients with low-SDF exhibited a significantly lower sperm concentration compared to those with high-SDF ($p=0.002$). There was significant down regulation of *TNP1* ($p=0.036$) and *PRM1* ($p=0.04$) in patients exhibiting high-SDF levels compared to those with low-SDF levels. A significant moderate positive correlation was observed between the relative expression levels of *TNP1* and *PRM1* ($r=0.459$, $p<0.001$).

Conclusion: In the present study *TNP1* and *PRM1* were differentially expressed in male patients being treated for infertility and who had low or high-SDF. (J Turk Ger Gynecol Assoc. 2025; 26: 7-14)

Keywords: Male infertility, *TNP1*, *PRM1*

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Introduction

Infertility is an important health problem in all countries. Almost 140 million people (around 15-18%) worldwide face infertility (1). Causative factors may be genetic, immunologic, hormonal, anatomic, teratogenic, infectious, smoking, exposure to radiation and others. It is a multifactorial condition and 25% of infertile couples have more than one factor (2). The cause of infertility may involve the female partner (1/3), male partner (1/3) or both (1/3). Around 15% of male infertility is caused by genetic factors (2,3), which can influence the spermatogenesis process, and may cause increased sperm anomalies (4).

Spermatogenesis, which begins after puberty, includes mitotic, meiotic and cellular reorganization. As a result of spermatogenesis, spermatozoa are formed, which enable the transmission of the male genetic material. During spermatogenesis, cell cycle checkpoints remove spermatocytes that harbor damaged DNA. Spermatocytes with undamaged DNA are allowed to continue spermatogenesis (5).

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Spermatozoa are highly differentiated cells consisting of three parts: the tail, the mid-piece and the head. Head of the sperm delivers the haploid genome into the oocyte during fertilization. Sperm cells are critical for the oocyte genome and vision (6). Chromatin condensation is important to minimize damage to sperm DNA during its passage through the male and female and reproductive tracts (7).

Another factor that has a significant place in male infertility is sperm DNA fragmentation (SDF) (8). Apoptosis, protamination disorders, and reactive oxygen species stand out as significant contributors to sperm DNA damage (9). SDF tends to increase with age, almost doubling in the 60s compared to the 20s (10). SDF can cause early pregnancy loss, and also may be an indicator in patients who cannot achieve pregnancy after assisted reproductive technology treatment or have a low fertilization rate (11). Although fertilization ability would not be lost in the case of SDF, it can negatively affect developmental stages of the embryo and result in genetic anomalies in the offspring (12,13). During the spermatogenesis process, the formation of a compact DNA occurs when transition proteins and protamines (PRM) replace histone proteins (14). In this multistage process, somatic cell histones undergo replacement with sperm PRM (15). This process begins with the substitution of histones by transition nuclear proteins (TNP) in round spermatids, followed by the subsequent replacement of both TNPs with PRM in elongating spermatids. As a result of this histone-protamine exchange, chromatin becomes highly condensed while remaining transcriptionally inactive (16).

PRM compress sperm DNA to almost six times greater compactness than somatic cell DNA, ensuring that the sperm nucleus remains protected and stable (17). This compact DNA combined with the mobile structure of the cell, provides an excellent vehicle for the genetic material it will carry to form the zygote (18).

The *TNP1* gene is a member of the *TNP* family and is abundantly expressed during spermatogenesis. Positioned on chromosome 2, *TNP1* encodes transition proteins (TP1 and TP2) (19). TP proteins are important since they reduce breaks during DNA condensation (20). Thus, *TNP1* plays a role in chromatin condensation. Defects in TPs may lead to atypical condensation of sperm chromatin, impaired motility of spermatozoa and increased frequency of breaks in sperm DNA strands (21,22). In another study, *TNP1* expression levels were examined for increased sperm DNA damage due to smoking and it was observed that *TNP1* gene expression was downregulated in cases with high sperm DNA damage (23).

PRMs, another sperm nuclear protein, is abundant in many species (24). The genes for PRMs (*PRM1* and *PRM2*), are located on chromosome 16p13.13, which forms a multigenic cluster (25). The *PRM* genes code the P1 and P2 proteins. P1 and P2 are synthesized as mature and precursor, respectively (26). PRM, which are rich in cysteine and arginine, have a special structure responsible for sperm chromatin condensation (27). Functions, such as production of a condensed genome with a hydrodynamic and compact nucleus, increase in transcription factors and other proteins during spermatid development, participation in paternal genome imprinting, being part of a checkpoint during spermatogenesis and playing a role in fertilization are some of functions of PRMs (15). The role of *PRM1* in male infertility is not fully understood (28). A recent study found that the level of *PRM1* gene expression is associated with reproduction (29).

Moreover, protamination is an important epigenetic regulatory process (30). Protamination results in the removal of histone-bearing epigenetic signals. This implies a role for protamination in the regulation of spermatozoa epigenetically. Epigenetic factors are active in the post-fertilization regulation of transcription. Histone modification and DNA methylation are potential mechanisms that may be involved in epigenetic regulation (23). Kläver et al. (31) found that there was a significant correlation between male infertility and increased levels of DNA methylation profiles in repressed genes.

For successful fertilization to take place, both sperm and egg need to possess the capacity to initiate key molecular mechanisms that can lead to viable embryonic development. In this regard, numerous studies have indicated that over 80% of fertilization failures in assisted reproductive treatments are linked to sperm-related issues (32). Studies have examined the impact of sperm protamine deficiency in fertilization failure (33,34) and the relationship between protamine imbalances in the sperm nucleus (35) and sperm DNA damage (36). In the present study, the goal was to evaluate *PRM1* and *TNP1* gene expression in cases with and without sperm DNA damage to understand the relationship between protamine expression and male infertility. Thus, the present study evaluated *TNP1* and *PRM1* gene expression in male infertility patients with low and high-*SDF*. The null hypothesis was that there was no significant difference in *TNP1* and *PRM1* gene expression levels between low and high-SDF groups.

Material and Methods

Participants were male infertility patients who applied to a genetic diseases evaluation center (Microgen, Ankara, Türkiye). Semen samples were taken from each subject. Semen samples were obtained from male participants undertaking treatment with intracytoplasmic sperm injection (Gen-Art IVF Center). Participants included in the current study were between the ages of 25 and 49 years. Informed consent form was given by all participants. A physical examination was performed on the participants. Responses were recorded with a structured

questionnaire covering the participants' medical history, occupation, and lifestyle.

The duration of abstinence from ejaculation for all participants was between 3 and 7 days. Samples were obtained by masturbation. The semen sample was diluted with 1X PBS Solution in a 5 mL Polystyrene Round Bottom tube to obtain a sperm concentration of $3x10^6$/mL. The samples were centrifuged at 2400 rpm for 5 minutes. 1X PBS Solution (1 mL) was added to the pellet and centrifuged again at the same time and speed. Then 1 mL of 4% paraformaldehyde solution stored at -20 °C was added to the pellet. The sample was fixed at +4 °C.

Criteria for inclusion and exclusion of patients

Criteria for inclusion of the current study were male infertility patients aged between 25 and 49 years. Patients with a history of cancer treatment, genetic disorders, hypogonadism or cryptorchidism were excluded.

Ethical approval and sample size determination

The protocol of the current study received approval from the ethics board of Biruni University Non-Interventional Clinical Research Ethics Committee (approval number: 2023/77-28, date: 06.01.2023). Based on data from the study of Amor et al. (23), 98 patients were found to be sufficient for the present study (power: 0.80%, significance level: 0.05, effect size: 0.506). Considering potential drop-outs, it was planned to enroll 100 patients.

TUNEL assay

The procedural steps for this test were conducted in accordance with the manufacturer's instructions (TUNEL kit; Roche Diagnostics GmbH, Germany). Following the washing and fixation protocol, 50,000 cells were analyzed (37). The patients were divided into two groups. Low-*SDF* group (n=50): having <16.8% TUNEL positivity and high-*SDF* group (n=50): having ≥16.8% TUNEL positivity.

Isolation of RNA

First, β-mercaptoethanol (240 μL) was added to each specimen. Vortex was used for mixing specimens. The specimens were then incubated at room temperature for 15 minutes with the lid closed. After incubation, 400 μL of 100% ethanol was added and the specimen was mixed by vortex for 40 s. Samples mixed with vortex were withdrawn without removing tissues and transferred to spin columns with brief patient information. Spin columns were centrifuged at 13000 rpm for 1min 30 s.

After centrifugation, the collection tubes were emptied and 400 μL RNA wash buffer was added onto the spin columns. By using purified semen specimens, total RNA isolations were performed according to manufacturer's recommendations of ZYMO RESEARCH Quick-RNA™ MiniPrep Kit. The quantity and purity of the isolated RNA were assessed using the NanoDrop spectrophotometer (Thermo Scientific, USA). Absorbance spectrophotometric ratio was at 260/280 nm.

Reverse transcription and quantitative PCR

Manufacturers' recommendations were followed when performing all procedures. The expression levels of *TNP1* and *PRM1* were measured using a real-time quantitative polymerase chain reaction (RT-qPCR) technique. The MiScript (Qiagen, Hilden, Germany) reverse transcription kit was used to convert total RNA to *cDNA* in a 10 μL reaction volume. Take 10 μL of each RNA sample and place it in 0.2 PCR tubes. The specimens were denatured for 5 minutes at 65 °C and then immediately placed on ice for 2 minutes to stop the process. Then, the master mix procedure was undertaken (LightCycler® 480 Roche Device). Each run included a no-reverse transcriptase control and a no-template control. Whole qPCR tests were conducted in duplicate, and the Ct values were normalized to GAPDH. MiScript reverse transcription kit was used to convert total RNA into c*DNA* (a reaction volume of 30 μL) (Qiagen, Hilden, Germany). Briefly, a mixture was made using 300 ng of isolated RNA, RNase-free water, miScript Reverse transcriptase mix, miScript HiFlex Buffer (5×), and miScript nucleic mix. The mixture was incubated in a thermocycler at 37 °C for 60 minutes, followed by incubation at 95 °C for 5 minutes to deactivate the transcriptase mix.

qPCR was conducted using the StepOnePlus™ System (7500 Fast Applied Biosystems, USA). The generated c*DNA* served as the template for qPCR analysis, conducted with SYBR Green and QuantiTect primer assay (Qiagen GmbH, Hilden, Germany), following the manufacturer's instructions. Each run included a no-template control and a no-reverse transcriptase control. Whole qPCR tests were conducted in triplicate, and the Ct values were standardized to GAPDH. Relative RNA quantity in the samples was assessed individually using the comparative ΔCt method, with the threshold cycle (Ct) indicating the cycle number at which the fluorescence curve intersects the qPCR threshold.

Statistical analysis

All statistical analysis were performed by using IBM SPSS 22 (Chicago, IL, USA) at 95% confidence level ($p<0.05$). Data were firstly analyzed with Kolmogorov-Smirnov test to understand whether the data normally distributed or not. Independent samples t-test were used to analyze age data. Mann-Whitney U test were used to analyze *TNP1*, *PRM1*, sperm concentrations and DNA damage percentage data. The Spearman correlation test was used to determine whether there was a correlation between the relative expression of the *TNP1* and *PRM1*.

Results

The consort flow diagram for patient selection can be seen in Figure 1. A total of 374 patients were eligible for the study, however, 100 met inclusion criteria. Laboratory processing failure occurred in seven of these patients. One of these was in the low-*SDF* group and six were in the high-*SDF* group.

There were no significant differences between the groups in terms of age. Table 1 presents sperm concentration, percentage of DNA damage, relative amount of *TNP1* and *PRM1* by group. In patients with low-*SDF*, sperm concentration was significantly lower than those with high-*SDF* (p=0.002). Moreover, there was significant down regulation of *TNP1* (p=0.036) and *PRM1* (p=0.04) in patients exhibiting high-SDF levels compared to those with low-SDF levels. A significant moderate positive correlation was observed between the relative expression levels of *TNP1* and *PRM1* (r=0.459, p<0.001).

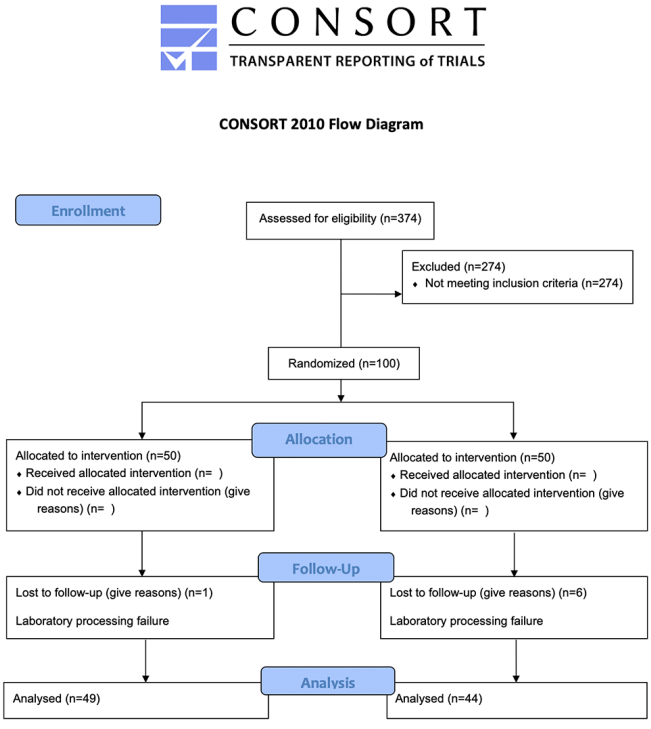

Figure 1. Consort flow diagram

Discussion

The present study aimed to evaluate *TNP1* and *PRM1* gene expression in male infertility patients with low and high-*SDF*. The relative amounts of the mRNA of *TNP1* and *PRM1* genes were differentially expressed between low and high-*SDF* groups. Thus, the null hypothesis was rejected. *TNP1* gene expression was down-regulated in patients with high-*SDF* compared to patients with low-*SDF*. Yu et al (38) conducted a study on mice by deleting the *tnp1* gene. Deletion of this gene affected sperm morphology and motility and also caused male infertility.

The general assumption was that *TNP*s are integrated into chromatin after histones are removed and that they act as intermediates between histones and PRM, since they constitute a significant portion of the genome in elongating spermatids (39). Several studies have highlighted the importance of *TNP1* in male infertility (40-42). Firstly, *TNP1* is essential for producing healthy sperm (42). Secondly, a considerable portion of men lacking *TNP1* are diagnosed as infertile due to severely diminished sperm motility (38). Knockdown of *TNP1* can cause abnormal sperm morphology and decreased progressive motility, leading to male infertility (38). Besides their role in *DNA* compaction, *TP1* and *TP2* are implicated in repairing DNA breaks that naturally occur during chromatin remodeling in the spermatid nucleus (43,44). There are studies showing that the disappearance of single strand breaks is consistent with the presence of transition proteins in elongating spermatids (45). TP1 is also able to stimulate intermolecular ligation of double-stranded breaks in DNA (46).

Histone and protamine substitution results in a transcriptionally dense and silent chromatin (16). Many studies have shown that an abnormality in protamine expression has a direct relationship with male infertility (36,47-49). A direct relationship between sperm protamine deficiency and fertilization failure has also been demonstrated in studies (34,50-52). Successful

Table 1. Comparison of the studied parameters between low and high sperm DNA fragmentation groups

	Patients with low sperm DNA fragmentation	**Patients with high sperm DNA fragmentation**	**p**
	(n=49)	**(n=44)**	**NA**
Age (years)	36.02±5.30	35.52±4.66	0.634
Relative amount of *TNP1*	-0.12±3.76	1.60±5.02	**0.036**
Relative amount of *PRM1*	-2.64±2.89	-0.37±4.31	**0.04**
Sperm concentration	47489795±35278724	33900000±48246392	**0.002**
Percentage of DNA damage	8.28±3.44	23.01±7.18	**<0.001**
NA: Not applicable, DNA: Deoxyribonucleic acid, TNP1: Transition nuclear protein 1, PRM1: Protamine 1			

fertilization necessitates the coordinated initiation of a series of events between the sperm and egg components, crucial for normal embryonic development. Both the sperm and egg must possess structural and genetic competence for successful fertilization to take place. The initiation of oocyte activation, and the fusion of oocyte and sperm chromosomes after fertilization, is mediated by sperm nuclear decondensation factors (53,54).

Fertilization failure is a frequent occurrence, observed in around 30% of oocytes following intracytoplasmic sperm injection in assisted reproductive treatments. Although more than 80% of unsuccessfully fertilized oocytes were released into the sperm using the microinjection technique, fertilization failure was attributed to the lack of biochemical mechanisms that initiate activation in the oocytes (55). Despite these deficiencies, the process may not start, or even if it starts, it may not proceed normally. It is caused by incomplete activation of sperm factors (56-58). Sperm morphology, sperm nuclear morphology, some changes in sperm chromatin and acrosomal defects are some of the sperm morphology-related factors in fertilization failure (34,59,60).

Recent studies suggest that the presence of unrepaired DNA damage surpassing a critical threshold in embryos, whether generated *in vivo* or *in vitro*, could explain the developmental halt observed post-implantation in embryos with a normal karyotype. Such damage is thought to occur during or after implantation and is characterized as a late paternal effect (61,62). In addition, there are indications suggesting a heightened level of DNA damage in sperm samples where a blastocyst cannot be obtained (63).

Dysregulated DNA methylation is very common in male infertility cases. There is a negative correlation between methylation and sperm DNA damage (64). Post-translationally modified histones are present in the sperm head fraction. This preserves epigenetic memory and facilitates epigenetic reprogramming of the zygote. Moreover, the process of protamination, which includes protamine phosphorylation and acetylation, may also play a role in this epigenetic process (65). While approximately 85% of histones are replaced with PRM during spermiogenesis in humans, epigenetic modifications, such as acetylation and methylation, are considered to be prevented by the remaining histones (66,67).

These findings underscore the multifaceted role of sperm cells beyond their primary function of transferring paternal DNA to the oocyte. The distinctive chromatin structure, which harbors epigenetic markers on genes implicated in transcription regulation and developmental processes, implies a significant involvement of the paternal genome in these crucial processes (67). In consideration of these insights, using sperm with protamine abnormalities during intracytoplasmic sperm injection may pose significant concerns for the developing embryo (68). Consequently, such circumstances may potentially lead to epigenetic alterations (69).

Another important role of protamine is to condense DNA, safeguarding its integrity by rendering the father's genetic contribution inaccessible to nucleases and mutagens (70). Consequently, anomalous protamine expression and dysregulated sperm chromatin might disturb processes associated with these functions, potentially affecting the transmission of paternal genetic material, resultig in negative impacts on embryo development. Indeed, deviations in the protamine composition within sperm nuclei have been associated with increased vulnerability to DNA damage (35).

Smoking and hookah use have been shown to cause increased *SDF* (23,71). Although direct comparison cannot be made between these studies and the results of the present study, these earlier findings should be noted. Amor et al. (23) reported that the expression of *TNP1* and *PRM1* were down-regulated in the spermatozoa of heavy smokers compared to non-smokers. Tofighi Niaki et al. (71) reported a trend in the decrease of *PRM1* expression among hookah smokers compared to controls (3.49±5.41 and 1.22±1.96), although the reduction did not reach significance.

Finally, we found that the relative level of *TNP1* expression moderately positively correlated with *PRM1* expression. This finding is in accordance with the findings of a previous study (23).

Numerous reports indicate a direct association between abnormalities in protamine expression and male infertility (36). Studies have demonstrated that round-headed spermatozoa from infertile patients contain lower levels of protamine and higher levels of histone and intermediate proteins compared to normal spermatozoa (71). This suggests that chromatin organization and acrosome formation occur at late stages of spermiogenesis.

The most common cause of male infertility is abnormalities in chromatin condensation, demonstrating how important chromatin condensation is (72). First, *TNP1* and *TNP*2 are replaced by histones, and then *PRM1* and *PRM2* are replaced by *TNP*s. These processes ensure the compression of the chromatin that will occupy the sperm head (73). In the current study, *TNP1* and *PRM1* genes, which have very important functions during chromatin condensation, were studied in patients with low and high-*SDF*. Sperm *DNA* damage can result from incomplete chromatin condensation. Sperm *DNA* damage serves as an indicator of low fertilization rates and an inability to achieve pregnancy. It can lead to early pregnancy loss and diminish the likelihood of clinical pregnancy in *in vitro* fertilization procedures (11,74). The results of the current study uncovered a significant down-regulation in *TNP1* and *PRM1* gene expression in individuals with high-*SDF* compared to those with low-*SDF* levels. This down-regulation may lead

to incomplete chromatin condensation, thereby contributing to sperm DNA damage. Benchaib et al. (75) and Borini et al. (37) used the same technique for sperm preparation as was used in the present study, and threshold values for the TUNEL assay were used as 20%. However, in a recent study by Sharma et al. (76), it was concluded that high specificity and positive predictive value was obtained at a cutoff point of 16.8%. Thus, threshold value of 16.8% for TUNEL assay was chosen in the present study.

Conclusion

In the present study *TNP1* and *PRM1* were differentially expressed in male patients being treated for infertility and who had low or high-SDF. Both of these genes were significantly down-regulated, based on mRNA levels, in male infertility patients with high levels of SDF compared to infertile peers with low-SDF levels.

Ethics

Ethics Committee Approval: *The protocol of the current study received approval from the ethics board of Biruni University Non-Interventional Clinical Research Ethics Committee (approval number: 2023/77-28, date: 06.01.2023).*

Informed Consent: *Informed consent form was given by all participants.*

Footnotes

Author Contributions: *Surgical and Medical Practices: Y.Ş., E.S.A., S.A., V.B., Concept: Y.Ş., E.S.A., S.A., V.B., Design: Y.Ş., E.S.A., S.A., V.B., Data Collection or Processing: Y.Ş., E.S.A., S.A., V.B., Analysis or Interpretation: Y.Ş., E.S.A., S.A., V.B., Literature Search: Y.Ş., E.S.A., S.A., V.B., Writing: Y.Ş., E.S.A., S.A., V.B.*

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Evaluation of the efficacy of injectable platelet-rich fibrin in genitourinary syndrome of menopause

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Abstract

Objective: The aim of this study was to investigate the efficacy of injectable, platelet-rich fibrin (PRF) for the treatment of vaginal atrophy, also known as genitourinary syndrome of menopause (GSM), which may affect a third of a woman's lifespan.

Material and Methods: This study included postmenopausal patients who had symptoms of genitourinary syndrome, such as vaginal burning, dryness, itching, and sexual dysfunction. Injectable platelet-rich fibrin (i-PRF) was applied to three areas on the posterior vaginal wall twice, one month apart. The genitourinary symptoms of the patients were evaluated using the female sexual function index (FSFI) and sexual life quality questionnaire before and one and six months after the procedure.

Results: Thirty-five patients were recruited with a mean age of 54.1±5.5 years. The analysis of the desire, arousal, lubrication, orgasm, satisfaction, pain, and total scores of the pre-procedural and post-procedural FSFI and sexual life quality questionnaire scores revealed significant improvements ($p<0.001$).

Conclusion: i-PRF treatment provided advantages such as safe and easy application, autologous material nature, absence of procedure-related complications or side effects, short procedure time, absence of the need for hospitalization, low cost, and a non-hormonal nature. These results suggest that injectable, PRF may be a promising treatment option in patients with symptoms of GSM. However, larger randomized controlled studies are needed to confirm and validate our findings. (J Turk Ger Gynecol Assoc. 2025; 26: 15-9)

Keywords: Female sexual function, genitourinary syndrome, injectable platelet-rich fibrin, menopause, minimally invasive therapy

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Introduction

Changes in the vulva, vagina and urinary system due to a hypoestrogenic state resulting from the loss of ovarian function in the menopausal period are called vulvovaginal atrophy. However, it has been suggested that this term does not fully correspond to the symptoms. Therefore, the terminology was changed to genitourinary syndrome of menopause (GSM) at the annual meetings of the International Society for the Study of Women's Sexual Health and The North American Menopause Society (1,2).

Symptoms of GSM include dyspareunia, vaginal dryness, loss of lubrication, friable vaginal epithelium, vaginal bleeding and discharge, vestibular discomfort, vulvar burning and itching, urethral sensitivity, dysuria, urinary urgency, recurrent urinary tract infections, and sexual dysfunction of arousal and orgasm (3). These symptoms of GSM occur in more than 50% of postmenopausal women, having a negative impact on quality of life, social activity and sexual relationships (4). Various treatment modalities for GSM have been described (5-7). These include hormonal and non-hormonal methods, such as vaginal moisturisers, lubricants, and platelet concentrates.

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Platelet rich plasma (PRP) is a first-generation platelet concentrate that appears like a weak fibrin mesh after the activation of centrifuged blood with thrombin and calcium (8). The additional use of anti-coagulants, which are found in PRP have been demonstrated to inhibit the wound healing process (9). Due to the disadvantages of PRP, platelet-rich fibrin (PRF) emerged as the second-generation equivalent blood product. Autologous 100% natural PRF is obtained by centrifuging blood without adding any anticoagulant (10,11). Compared to PRP, PRF releases a greater amount of growth factors which makes it perfect for stimulating tissue regeneration and growth (10). Injectable platelet-rich fibrin (i-PRF), the liquid preparation of PRF, has more platelets, white blood cells and a greater degree of cellular migration than PRF (12). However, it has been reported that there are side-effect and cost considerations when using PRF (13). In the present study, we aimed to investigate the efficacy of i-PRF in women with GSM (13). There have been studies examining the use of PRP in GSM (14,15). However, we were unable to find any publications investigating the efficacy of i-PRF for GSM.

Material and Methods

This study was carried out from May 2021 to July 2022 at a outpatient clinics of Obstetrics and Gynecology Department of a University Hospital. The study was approved by the Bolu Abant İzzet Baysal University Local Ethics Committee (approval number: 2021/103, date: 27/04/2021) and performed in accordance with the Helsinki Declaration. Postmenopausal women suffering from one or more GSM symptoms were included to the study. Prior to enrolment and treatment, all patients were informed of the study's purpose and methodology and provided written informed consent.

Asian patients who did not have any gynecological pathology, had started natural menopause at least three years prior to the study, and were sexually active heterosexuals were included in the study. Women with a diagnosis of metabolic and/or chronic inflammatory diseases, who had undergone gynecological abdominal or vaginal surgery, were using hormone replacement therapy, smokers, had an active vaginal infection, or had previously undergone vaginal treatment (such as with hyaluronic acid) for GSM were excluded from the study.

An 18 mL blood sample was withdrawn from each patient and put into two i-PRF tubes. The blood samples were then centrifuged at 700 rpm for 3 minutes (16). The upper layer of the tube was aseptically withdrawn into a syringe. The patients were positioned in the lithotomy posture and the i-PRF preparation was immediately injected at three different lateral points, side-by-side at 0.5-1 cm intervals into the posterior vaginal wall, 2-3 cm above the vaginal forchete. Approximately 1-2 cc i-PRF solution was injected at each point. The procedure was performed using 26 G 0.45 mm insulin syringes. The procedure was repeated twice with a 1-month interval.

The patients were interviewed face-to-face and evaluated using the Female Sexual Function Index (FSFI) and sexual life quality scale (SLQQ) questionnaires before the procedure and one month and six months after the i-PRF application.

The FSFI questionnaire consists of 19 close-ended questions related to sexual activity within the four weeks prior to the examination and includes six domains: sexual desire (questions number 1-2), sexual arousal (questions number 3-6), lubrication (questions number 7-10), orgasm (questions number 11-13), satisfaction (questions number 14-16) and pain (questions number 17-19). Points are assigned for each answer (1-5 and 0-5 for questions 1-2 and questions 3-19, respectively), the sum of the scores for the domain is multiplied by the domain factor, the six domain scores are added up, and the total score may vary from 2.0 to 36.0 points. The effect coefficients used for scoring the whole scale are 0.6 for sexual desire; 0.3 for sexual arousal and lubrication; and 0.4 for orgasm, satisfaction, and pain/discomfort. A score lower than 26.55 was interpreted as indicating a risk of sexual dysfunction (17).

In the present study, the satisfaction level of the participants was also evaluated using the SLQQ. This scale is scored using a six-point Likert type and consists of 18 items. Each item is expected to be answered considering sexual life in the last four weeks. The scale is evaluated by scoring each item with a score of 1-6 (1: I totally agree; 2: I largely agree; 3: I partly agree; 4: I partly disagree; 5: I largely disagree; 6: I totally disagree). The range of score of the scale is 18-108. In this scoring system, the total score obtained from the scale is converted to 100. It is reported that the formula (the raw score obtained from the scale-18, x100/90) must be used to convert the total scale score to 100. A high score indicates a good quality of sexual life (18).

Statistical analysis

The study data were analyzed using SPSS Statistics, version 26 (IBM Corp., Armonk, NY, USA). The descriptive statistics are presented as number of units (n), percentage (%), mean ± standard deviation mean (x ± SD), and/or median (M), minimum value and maximum value. Normality of scale score distribution was evaluated with skewness and kurtosis measures. For all difference scores, the kurtosis and skewness values were between -1.96 and 1.96, which proved that the data were normally distributed. The scale scores of all participants before the procedure and 1 month and 3 months after the procedure were analyzed using one-sided analysis of variance. The participants scale scores for body mass index (BMI), mode of delivery, and educational status before and 1 month and three months after the procedure were analyzed using two-sided analysis of variance for repeated measurements.

Bonferroni correction was used for all paired comparisons in analyses of variances in repeated measurements. A $p<0.05$ was considered statistically significant.

Results

A total of 35 postmenopausal women were included in this study, with the mean age of 54.15.5± years, ranging from 44-68 years and mean BMI was 29.68±6.79 kg/m^2, ranging 20.30-43.20. Thus less than a third (31.4%) exhibited normal weight while 37.2% were classified as obese. The duration of menopause was between 3 and 16 years, with a mean of 7.5±3.6 years. More than three-quarters (77.1%) had experienced at least one vaginal delivery. Demographic characteristics of the cohort are shown in Table 1.

There was an improvement in all parameters in the FSFI questionnaire after treatment (Table 2). Desire, arousal, lubrication, orgasm, satisfaction, pain, and total FSFI scores exhibited significant improvements. The scores of both the first and sixth months after the procedure were higher than the pre-procedure scores. However, there was no significant differences between the scores in the first and sixth months after the procedure.

Similarly, SLQQ questionnaire scores demonstrated significant improvement after i-PRF injection. Scores in the first and sixth months after the procedure were significantly higher than the pre-procedure scores. However, again there was no difference between the first and sixth months scores after the procedure (Table 3).

Table 1. Demographic data

Variables (n=35)	
Age (years)	54.1±5.5
BMI (kg/m^2)	29.68±6.79
Duration of menopause (years)	7.5±3.6
Number of children n (%)	
None	3 (8.6%)
One	2 (5.7%)
Two	18 (51.4%)
Three	7 (20.0%)
Four	5 (14.3%)
Mode of delivery n (%)	
None	3 (8.6%)
Normal	23 (65.7%)
Cesarean	5 (14.3%)
Normal + cesarean	4 (11.4%)
Educational status n (%)	
Illiterate	3 (8.6%)
Primary school	19 (54.3%)
High school	9 (25.7%)
University	4 (11.4%)
BMI: Body mass index	

Discussion

The diagnosis and treatment of the GSM are important for preventing progression and deterioration of the quality of life and sexual health. GSM affects from 40 to 54% of postmenopausal women (19). Alternative treatment methods, such as hyaluronic acid, laser and PRP are gaining popularity for the treatment of patients with GSM symptoms, such as breast and endometrial cancer, who cannot receive hormone therapy and who do not want to use hormone therapy (20). In the present study, vaginal i-PRF injection was found to be effective for improving symptoms of GSM.

PRP is a first-generation thrombocyte concentrate that is used as a regenerative agent. Compared to PRP, PRF has a higher wound healing enhancing effect because it releases a greater amount of growth factors. PRF stimulates tissue regeneration and growth by providing stable and constant release of the growth hormone and cytokines in the tissue. The advantage of PRF over PRP is that it is 100% natural and has no side effects because it is prepared without using anticoagulants or other biochemical additives.

PRF contains a larger number of white blood cells and thrombocytes, which are the key cells in wound healing, and a larger amount of fibrin. Thrombocytes provide regional activation of macrophages and neutrophils by releasing cytokines and growth factors (21). Leucocytes protect the wound against infections during wound healing and regulate the immune system by releasing cytokines, such as interleukin 1-beta (IL-1β), IL-6, IL-4, and tumor necrosis factor-alpha (22). Since PRF locks cytokines, glycolic chains, and structural glycoproteins in polymerized fibrin mesh, it affects the extracellular matrix, thereby promoting a reaction chain of endothelial cell migration, dislocation, and phenotype change, which ultimately results in new vessel formation (10).

i-PRF is the liquid form of PRF, and its three-dimensional fibrin content forms a system for regular release of growth factors. Due to this characteristic, i-PRF produces an excellent PRF thrombus substitute. Historically, the primary use of i-PRF was in oral maxillofacial surgery; however, its use has demonstrated significant success in both surgical and non-invasive esthetic procedures, leading to increased use in both esthetic and reconstructive medicine (23-25).

i-PRF has been used for skin rejuvenation, and the results indicated significant improvement due to its important regenerative functions, including stimulation of fibroblast proliferation through the mesenchymal stem cell pathway, enhanced anti-inflammatory effects, angiogenesis, and protein

Table 2. FSFI scores before treatment and 1, 6 months after treatment

FSFI	Pre-procedure	Post-procedure 1st month	Post-procedure 6th month	p
Desire	1.98 ± 0.9^{X}	2.97 ± 0.92^{Y}	2.71 ± 1.18^{Y}	**<0.001**
Arousal	1.56 ± 0.9^{X}	3.12 ± 1.20^{Y}	2.99 ± 1.30^{Y}	**<0.001**
Lubrication	1.26 ± 0.7^{X}	3.32 ± 1.34^{Y}	3.14 ± 1.45^{Y}	**<0.001**
Orgasm	1.35 ± 0.9^{X}	3.09 ± 1.31^{Y}	2.84 ± 1.27^{Y}	**<0.001**
Satisfaction	1.35 ± 0.8^{X}	3.06 ± 1.38^{Y}	2.99 ± 1.58^{Y}	**<0.001**
Pain	1.16 ± 0.7^{X}	3.45 ± 1.38^{Y}	3.21 ± 1.66^{Y}	**<0.001**
Total score	8.72 ± 4.5^{X}	19.04 ± 7.08^{Y}	17.88 ± 8.14^{Y}	**<0.001**

The data are summarized as mean ± SD. *One-sided analysis of variance in repeated measures. The upper case letters "X" and "Y" denote a significant difference between measurements. There is no statistical difference between the measurements denoted by the same letter. FSFI: Female sexual function index

Table 3. SLQQ scores before treatment and 1, 6 months after treatment

	Pre-procedure	Post-procedure 1st month	Post-procedure 6th month	p
SLQQ	35.15 ± 9.25^{X}	44.45 ± 11.3^{Y}	46.84 ± 13.7^{Y}	**<0.001**

The data are summarized as mean ± SD. *One-sided analysis of variance in repeated measures. The upper case letters "X" and "Y" denote a significant difference between measurements. There was no statistical difference between the measurements denoted by the same letter. SLQQ: Sexual life quality scale

accumulation for extracellular matrix remodeling through leukocytes (24). Furthermore, due to its ability to attract epithelial cells and facilitate microvascularization, PRF has the capacity to protect open wounds and expedite healing. Therefore, the application of PRF for periodontal diseases, particularly in dental root coverage, has become increasingly popular (25).

In a study conducted in 2024, the effects of i-PRF on stress urinary incontinence were investigated. Three consecutive i-PRF injections at one-month intervals into the mid-urethral location of the anterior vaginal wall was shown to effectively alleviate symptoms of stress urinary incontinence with high success rates, without any reported side effects (13).

Neto (26) recorded a decrease in the severity of dyspareunia and urinary incontinence after vaginal PRP injection. Runels et al. (14) performed a similar study with a single application and found a decrease in the rate of sexual dysfunction. Sukgen et al. (15), in a study involving 52 patients analyzed the effects of PRP injection to the anterior vaginal wall on genital perception in women with impaired orgasm and sexual dysfunction. These authors found an increase in the FSFI score and a high satisfaction level (15). Aguilar et al. (27) assessed the quality of sexual life after injecting hyaluronic acid and PRP to the posterior vaginal wall and reported a positive impact of the treatment in these patients. It was shown that symptoms of GSM significantly improved following hyaluronic acid and PRP injection in a study including 236 women (19). Similarly, a study found that PRP treatment could be used not only for the treatment of urinary incontinence, but also to treat the symptoms of vaginal fistula and the genitourinary syndrome (28). Numerous studies have shown that PRP (14,15,27) are effective in treating GSM. However, we were unable to find any published study of the efficacy of locally administered i-PRF for GSM. In the present study, i-PRF was injected twice at one-month intervals to the posterior vaginal wall at three separate but close sites. We did not detect any adverse conditions such as bleeding, pain, or allergic reactions at the injection site after the procedure. Significant improvements were detected in scores reported by both the FSFI and SLQQ, although the total scores for FSFI indicated all women still maintained a risk of sexual dysfunction, based on previously reported cut-offs.

Study Limitations

The limitations of our study include the lack of a standardized application procedure for the dose, application frequency, injection site, and number of injections of i-PRF. In addition, the number of cases was low, and there was no control group. Finally, the follow-up period was relatively short at six months and one of the questionnaires used had indicated a continued improvement at six months, although not significantly better than at three months follow-up. The fact that more than 77% of the patients included in the study had a vaginal birth and the average BMI of the patients was 29 are the factors that may affect the interpretation of the study results.

Conclusion

This study demonstrated that i-PRF application provided a significant improvement in sexual quality of life among women

with GSM symptoms measured by two validated questionnaires. i-PRF, which promotes angiogenesis, tissue regeneration, and wound healing, may have a role in the treatment of GSM. However, there is a need for longer term, larger prospective studies. These should also investigate the effects after more and/or larger doses of i-PRF, potentially monitoring the changes in the vaginal wall with biopsy, and using different indices, such as the vaginal health index.

Ethics

Ethics Committee Approval: *The study was approved by the Bolu Abant İzzet Baysal University Local Ethics Committee (approval number: 2021/103, date: 27/04/2021).*

Informed Consent: *All patients were written informed consent.*

Footnotes

Author Contributions: *Surgical and Medical Practices: P.O., Ü.M.U., Concept: P.O., Ü.M.U., Design: P.O., Ü.M.U., Data Collection or Processing: P.O., Ü.M.U., Analysis or Interpretation: P.O., Ü.M.U., Literature Search: P.O., Ü.M.U., Writing: P.O., Ü.M.U.*

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The effects of non-functioning pituitary adenomas on pregnancy

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Abstract

Objective: Non-functioning pituitary adenomas (NFPAs) are a group of hormonally inactive adenomas. The aim of this study was to investigate the possible effects of NFPAs on pregnancy.

Material and Methods: Thirty patients with NFPAs and without hormone deficiency or excess were included. We retrospectively evaluated anterior pituitary hormone levels, follow-up periods, pituitary imaging findings, symptoms associated with adenoma size increase during pregnancy, adverse pregnancy outcomes, delivery procedures, pregnancy week at delivery, birth weight, and lactation duration.

Results: The mean age of the patients was 41.26±9.06 years, and the mean follow-up after diagnosis was 92.8 months. Seven were diagnosed with macroadenomas (defined as the largest diameter >10 mm) and 23 had microadenomas. There were 92 pregnancies in total. The incidence of nausea-vomiting and visual impairment during pregnancy were more common in the macroadenoma group (p=0.016 and p=0.042, respectively). Spontaneous pregnancy rates were high. The patients with NFPAs did not have an increased risk of pregnancy-related complications compared to the general population, and there were no obvious negative effects on fetal development or lactation. NFPAs were not associated with an increased cesarean section rate.

Conclusion: These findings suggest that NFPAs, even macroadenomatous NFPAs, have no negative effects on pregnancy outcomes, fetal development, or lactation. (J Turk Ger Gynecol Assoc. 2025; 26: 20-5)

Keywords: Pituitary, pregnancy, non-functioning pituitary adenomas, adenoma

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Introduction

Pituitary adenomas that are not hormonally active are referred to as clinically non-functioning pituitary adenomas (NFPAs). Pituitary adenomas are relatively common, with 80-100 cases per 100,000 population, with NFPAs making up 15-30% (1). Currently, NFPA is detected either because of the mass effect of a macroadenoma or, increasingly, incidentally during an imaging procedure, a condition known as pituitary incidentaloma (2). Pregnancy alters the structure and function of the pituitary gland. Due to lactotroph hyperplasia, during pregnancy the anterior and total pituitary volume significantly increase and remain larger in the first post-partum year (3). This growth may cause a risk of visual impairment, particularly with macroadenomas or adenomas close to the optic chiasm. In the event of the emergence of symptoms such as headache, visual impairment, ophthalmoplegia, nausea and vomiting, and altered consciousness, pituitary apoplexy, which is a rare but potentially life-threatening condition, should be considered as a potential diagnosis (4).

Research evaluating the relationship between NFPAs and pregnancy is fairly limited (4-6). The current guidelines recommend evaluating the size of the adenoma and its proximity to the optic pathways when considering surgery during the preconceptional period. This approach helps reduce the likelihood of adenoma growth and the risk of

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infertility. It has been stated that individuals with non-functional microadenomas do not require routine monitoring throughout pregnancy due to their low growth potential (7).

In this study, we aimed to investigate the impact of NFPAs on pregnancy and related conditions, focusing on aspects such as symptoms due to adenoma size during pregnancy, delivery procedures, adverse pregnancy outcomes, and lactation duration.

Material and Methods

The study was a retrospective cross-sectional design. The study population included patients with a diagnosis of benign neoplasm of the pituitary gland who presented to our institution between January 2009 and November 2022. Of 12,277 patient records initially screened (excluding male patients and duplicates), there were 1,906 female patients. Incomplete records, functional pituitary adenomas, and patients with hormonal deficiencies were excluded, based on clinical and laboratory findings. This resulted in an eligible study cohort of 119 patients with NFPA who met the inclusion criteria. The patient's understanding and confidentiality were discussed by calling the patients by phone and explaining the purpose, content and method of the study to the patient by the same physician throughout the interview. Of the 86 patients who were successfully contacted, those meeting any of the following exclusion criteria were removed from the study: male infertility in their spouse, polycystic ovary syndrome, infertility due to a tuboperitoneal anomaly, or uterine anomalies (either congenital or acquired). After applying these criteria, the remaining patients were fully informed about the study's objectives and methodology. Ultimately, 30 patients with NFPA who met the inclusion criteria and provided verbal informed consent were included in the final analysis.

The study collected various data from patients, including gestational age, presence of other diseases, regular medication use, duration of follow-up for NFPA before pregnancy, and the cycle in which pregnancy occurred after contraception. Patients were also asked about the method of conception (spontaneous or assisted reproduction). In addition to these data, patients were specifically questioned about symptoms experienced during pregnancy, particularly those suggestive of pituitary apoplexy. These included nausea and vomiting during the second and third trimesters, headache, ophthalmoplegia, visual impairment, and altered consciousness. Detailed information was gathered to determine the onset, severity, and progression of these symptoms, helping to better understand their relationship to adenoma size and potential growth during pregnancy. Furthermore, obstetric history was obtained, including gravida, parity, abortion, miscarriage, and live or stillbirth outcomes. Data on additional obstetric complications, such as gestational diabetes mellitus (GDM), pregnancy-related hypertension, and preeclampsia, were also collected. Delivery details (miscarriage, live birth, or stillbirth), gestational age at delivery, mode of delivery, newborn health, birth weight, and lactation duration were recorded for comprehensive analysis.

Statistical analysis

Data analysis was performed using the SPSS for Windows 15 software package (IBM Corporation, Armonk, NY, USA). The normal distribution of variables was assessed using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive statistics are presented as median and range for non-normally distributed variables, mean ± standard deviation for normally distributed variables, and number of cases and percentages for nominal variables. Fisher's exact test was used to compare categorical variables, while the Mann-Whitney U test was used to compare independent variables that were non-normally distributed between the two groups. Patients with macroadenoma, defined as an adenoma with the largest diameter of >10 mm, and microadenoma were compared using crosstabs for abortion, stillbirth, ectopic pregnancy, nausea, vomiting, headache, and visual impairment. Pearson's chi-square or Fisher's exact test was used depending on whether there was a difference between the groups regarding these frequencies and when the values observed in the cells did not meet the chi-square test assumptions. A significance level of $p<0.05$ was used to determine statistical significance.

Results

Of the 30 patients with NFPA, 7 (23.3%) had macroadenomas, and the longest median (range) diameter of these adenomas was 12 (11-18) mm, while 23 had microadenomas. Patients' current mean age was 41.3±9.1 years and NFPA follow-up duration was a mean of 92.8±56 months. In total there were 92 pregnancies recorded. Twelve (%) had undergone an elective abortion, three (%) cases were ectopic pregnancies (mean 7.3 weeks), seven (%) were missed abortions (mean 9.1 weeks), four (%) were stillbirths (mean 25 weeks), and 66 (%) resulted in live births.

Table 1 shows the characteristics of gestational age, birth weight, week of birth, lactation duration, adenoma-related symptoms, pregnancy complications, delivery method, and outcomes of live births. There were preterm births (before 37 completed weeks) in 21.2% of live births. Of all the live births, 9% were macrosomic, and 12% had low birth weight. Regarding lactation, the median duration was 18 (0-30) months, with 12% of patients having a lactation period of six months or less without an identifiable cause, and two pregnancies had no lactation.

Thirteen of the 92 pregnancies occurred in patients with NFPA before pregnancy. Among these patients, one experienced a missed abortion at 6 weeks, and the remaining 12 pregnancies resulted in live births. The characteristics and outcomes of these live births are presented in Table 2. The median duration from contraception withdrawal until conception was 2.5 (1-12) months, and no patient used assisted reproductive techniques. Preterm births occurred in two pregnancies, accounting for 16.6% of all live births, while low birth weight was observed in two infants (16.6%). None of the infants exhibited macrosomia.

Table 3 compares the rates of missed abortion, ectopic pregnancy, and stillbirth in the macroadenoma and microadenoma groups for all pregnancies except elective abortions. The incidence of missed abortion was 6.3% in the macroadenoma group and 9.4% in the microadenoma group (p=0.573). Ectopic pregnancy occurred in 0% of the macroadenoma group and 4.7% of the microadenoma group, but again this was not significant (p=0.507). Similarly, stillbirth occurred in 0% of the macroadenoma group and 4.7% of the microadenoma group, and the difference was not significant (p=0.507).

Table 4 compares the frequencies of symptoms in pregnancies resulting in live births between the macroadenoma and microadenoma groups. Nausea and vomiting were significantly more frequent in the macroadenoma group (28.6%) than in the microadenoma group (3.8%) (p=0.016). Vision impairment was significantly more common in the macroadenoma group (14.3%) than in the microadenoma group (0%, p=0.042). Headache was reported in 28.6% of the macroadenoma group and 17.3% of the microadenoma group, but the difference was not significant (p=0.450). The study also screened for signs of ophthalmoplegia, changes in consciousness, and apoplexy, and none were observed in any of the pregnancies.

The comparison of pregnancies resulting in a live birth for the week of birth, birth weight, and lactation period are shown in Table 5. The median birth weight was 3200 (2500-4500) grams in the macroadenoma group and 3500 (1200-4900) grams in the microadenoma group (p=0.551). The median birth week was 38.5 (35-40) weeks in the macroadenoma group and 39 (29-41) weeks in the microadenoma group (p=0.955). The median lactation period was 18 (0-30) weeks in the macroadenoma group, and 18 (2-24) weeks in the microadenoma group (p=0.786). Overall, none of the differences between the two

Table 1. Outcomes and characteristics of live births (n=66)

	Median	Minimum-maximum
Age of gestation (year)	23.5	16-38
Birth weight (grams)	3470	1200-4900
Week of birth (week)	39	29-41
Lactation duration (month)	18	0-30
	n	**%**
Nausea-vomiting	6	9.1
Headache	13	19.7
Vision impairment	2	3
Ophthalmoplegia	0	0
Altered consciousness	0	0
Apoplexy	0	0
Pregnancy-related complications		
Pregnancy-related hypertension	4	6.1
Preeclampsia	1	1.5
Gestational-diabetes mellitus	4	6.1
Birth method		
Spontaneous vaginal delivery	40	60.6
Cesarean section	26	39.4
In vitro fertilization	2	3
Insemination	1	1.5
Spontaneous pregnancy	63	95.45

Table 2. Characteristics and outcomes of live births of patients with known pre-pregnancy non-functional pituitary adenoma diagnosis (n=12)

	Median	Minimum-maximum
Age of gestation (years)	30	21-35
Pre-pregnancy follow-up period (months)	48	12-120
Total follow-up period (months)	120	36-252
Birth weight (grams)	3225	2300-3840
Week of birth (weeks)	38	35-40
Lactation duration (months)	14	2-24
	n	**%**
Nausea-vomiting	3	25
Headache	3	25
Vision impairment	1	8.3
Ophthalmoplegia	0	0
Altered consciousness	0	0
Apoplexy	0	0
Pregnancy-related complications		
Pregnancy-related hypertension	0	0
Preeclampsia	0	0
Gestational-diabetes mellitus	0	0
Birth method		
Spontaneous vaginal delivery	7	58.3
Cesarean section	5	41.6
In vitro fertilization	0	0
Insemination	0	0
Spontaneous pregnancy	12	100

Table 3. Comparison of outcomes of pregnancies except for elective abortion*

	Macroadenoma, (n=16)	Microadenoma, (n=64)	Total, (n=80)	p
	n (%)	n (%)	n (%)	
Missed abortion	1 (6.3)	6 (9.4)	7 (8.8)	0.573
Ectopic pregnancy	0 (0)	3 (4.7)	3 (3.8)	0.507
Stillbirth	0 (0)	3 (4.7)	3 (3.8)	0.507
*Column percentages are given. ** Fisher's exact test was used				

Table 4. Comparison of symptoms seen in pregnancies resulting in live birth*

	Macroadenoma, (n=14)	Microadenoma, (n=52)	Total, (n=66)	p
	n (%)	n (%)	n (%)	
Nausea-vomiting	4 (28.6)	2 (3.8)	6 (9.1)	**0.016****
Headache	4 (28.6)	9 (17.3)	11 (6.7)	0.450**
Vision impairment	2 (14.3)	0 (0)	2 (3.0)	**0.042****
*Column percentages are given. **Fisher's exact test was used				

Table 5. Comparison of pregnancy outcomes and lactation in patients with macroadenoma and microadenoma

	Macroadenoma, (n=14)	Microadenoma, (n=52)	p*
	Median (minimum-maximum)	Median (minimum-maximum)	
Week of birth (week)	38.5 (35-40)	39 (29-41)	0.955
Birth weight (gram)	3200 (2500-4650)	3500 (1200-4900)	0.551
Lactation duration (month)	18 (0-30)	18 (2-24)	0.786
*Mann-Whitney U test was used for comparison			

groups were significant for birth weight, birth week, or lactation period.

Discussion

There is limited data available on the relationship between NFPAs and pregnancy. To address this gap, we conducted a study to investigate the effects of NFPAs on pregnancy and related factors. We focused on examining symptoms caused by adenoma size during pregnancy, delivery procedures, adverse pregnancy outcomes, and lactation duration.

According to the Türkiye Demographic and Health Survey 2018 (TNSA-2018), from 2013 to 2018, 6% of pregnancies resulted in elective abortion, 13% in a missed abortion, 1% in a stillbirth, and 80% in a live birth (8). To assess the potential complications and mortality rates associated with childbirth, it is essential to consider the national data specific to the country, and we analyzed our data in this manner. Our findings suggest that NFPA does not significantly affect the rates of elective and missed abortions, as they were similar to the national averages. The incidence of stillbirths in the study population (4.3%) was higher than the national average (1%), but this was not significant and the cohort size was small. Confirmation of these data is needed, and if verified, additional research is required to investigate the underlying mechanisms. Twelve percent of all live births in our study were of low birth weight, a figure that mirrors the national rate of 12%; similarly, the average lactation duration in our sample was 16 months, closely aligning with the median breastfeeding duration of 16.7 months reported in national data. Nevertheless, caution must be exercised when interpreting these relationships, as the small sample size and the absence of detailed sociodemographic data may limit the generalizability of these findings. Thus, the results should be viewed as suggestive rather than definitive. This study highlights the need for further research, particularly into the potential impact of pituitary adenomas on pregnancy outcomes, as the current data, while informative, are not robust enough to fully elucidate the complexity of these associations.

Obstetric problems in the general population, such as GDM, occur at a rate of 0.06-15% (9), pregnancy-related hypertension occurs at a rate of 6-10% (10), and preeclampsia occurs at a rate of 3-5% (11). The rates in our cohort were similar to these figures in the general population. Regarding the chosen delivery method, 26 (39.4%) patients were delivered via cesarean section. Our national rate of elective Cesarean sections is higher at 47.5% (12). UK researchers found that 50% of individuals with NFPA underwent cesarean delivery, compared to 24% of the general population (4). However, our study did not find

any evidence of an increased risk of cesarean section in these patients, despite high rates nationally. The mean birth weight in our study was 3154 grams with a similar median value of 3225 grams, ranging from 2300-3840. It was 2500 g or less in only two cases (16.6%). Karaca et al. (5) reported that one in six live births (16.6%) were macrosomic, but no additional problems were detected. No adverse effects of NFPA on fetal development have been demonstrated.

An increase in the size of NFPAs has been reported on rare occasions due to tumor growth, infarction, or hemorrhage during pregnancy (4,6,13). Karaca et al. (5) performed an MRI of the pituitary in one patient, and the adenoma did not enlarge. No compression symptoms were observed during pregnancy. Comparing pregnancy characteristics between patients with macroadenoma and microadenoma, our data show no significant differences between the two groups regarding the frequency of missed abortions, ectopic pregnancies, and stillbirths. However, headaches were seen in 17.3% of the microadenoma group and 28.6% of the macroadenoma group. Although this difference was not statistically significant, the higher incidence in the macroadenoma group may be associated with adenoma enlargement caused by lactotroph cell hyperplasia during pregnancy and/or an increase in dural pressure caused by the macroadenoma, as reported in the literature (14). The significantly higher incidence of visual disturbances in the macroadenoma group may be due to optic chiasm compression. However, we did not observe apoplexy, altered consciousness, or ophthalmoplegia, which are rare complications reported in the literature. There were no statistically significant differences among live births in gestational age, birth weight, and duration of lactation between the groups. Our findings did not demonstrate a correlation between adenoma size larger than 10 mm, that is macroadenoma by definition, and unfavorable pregnancy outcomes.

There were 13 (14%) of 92 pregnancies occurred in patients who had a pre-existing NFPA before pregnancy. One of the pregnancies resulted in a missed abortion in the sixth week. No ectopic pregnancy or stillbirth was observed, and the remaining 12 pregnancies resulted in live births. The patient with the missed abortion had a microadenoma. Of the pregnancies that resulted in live births, three had macroadenomas, and nine had microadenomas. No symptomatic growth or mass effect was observed in any patients during pregnancy in our study. Although a size increase in NFPA is rare during pregnancy, visual loss and apoplexy have been reported (15,16). However, according to the literature and our study, the risk of symptomatic growth appears to be very low, especially in microadenomas (4,5,17).

The literature suggests that an NFPA can impact fertility and result in rare pregnancies due to the effects of gonadotropin production and hyperprolactinemia (18). In the study by Karaca et al. (5), spontaneous pregnancy occurred in seven patients (87.5%), one of whom was using cabergoline and six patients were receiving no treatment. In contrast, one secondary hypogonadism patient became pregnant with ovulation induction. Our high spontaneous pregnancy rates may be because patients with hypogonadotropic or hypergonadotropic hypogonadism and hyperprolactinemia were excluded, and only those with a normal hormone panel were included. Furthermore, there was a lack of data for women with NFPA who did not have to conceive. Consequently, our data is insufficient to conduct a thorough examination of the correlation between NFPA and fertility.

Study limitations

The most significant limitations of our study include the small sample size and the difficulty in accessing all data due to the retrospective design. Although the lack of a control group is a limitation, we compared our findings with national data. Furthermore, we excluded patients with hormonal abnormalities and a history of medical treatment to minimize confounding factors. This resulted in a selected population for evaluating the effects of NFPAs on pregnancy. Of the 66 pregnancies resulting in live births in our study, 13 were in women with a pre-existing diagnosis of NFPA, while the remaining 53 pregnancies occurred before the diagnosis. However, since all of these patients were asymptomatic, there may have been a delay in the diagnosis, and adenomas may have been present during the pregnancies.

Conclusion

This study indicated that symptoms suggestive of adenoma growth during pregnancy are more prevalent in patients with macroadenoma than in those with microadenoma. However, further research is necessary to establish whether these symptoms are an effect of the tumor growth. Our findings suggest that NFPAs did not have any adverse effects on pregnancy outcomes, fetal development, or lactation.

Ethics

Ethics Committee Approval: *The study received approval from the Ethical Committee of Ankara University Faculty of Medicine (approval number: İ5-227-19, date: 14.11.2019).*

Informed Consent: *Informed consent were obtained.*

Footnotes

Author Contributions: *Surgical and Medical Practices: Ö.B.A., Ö.D., A.G.C., D.Ç., Concept: Ö.B.A., Ö.D., A.G.C., D.Ç., Design: Ö.B.A., Ö.D., A.G.C., D.Ç., Data Collection or Processing:*

Ö.B.A., Ö.D., A.G.C., D.Ç., Analysis or Interpretation: Ö.B.A., Ö.D., A.G.C., D.Ç., Literature Search: Ö.B.A., Ö.D., A.G.C., D.Ç., Writing: Ö.B.A., Ö.D., A.G.C., D.Ç.

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Outcomes of emergency cervical cerclage after amnioreduction in twin pregnancies with a fully dilated cervix and amniotic membrane prolapse

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Abstract

Objective: The aim of this study was to evaluate the effectiveness of emergency cervical cerclage (EmC) in twin pregnancies with a fully dilated cervix and amniotic membrane prolapse.

Material and Methods: This retrospective study examined records from December 2015 to December 2022 and included 20 twin pregnancies. The patients were divided into two groups, the EmC group (EmC group) and the no EmC (control) group, and pregnancy outcomes were compared.

Results: EmC was performed after amnioreduction in 11 twin pregnancies. Nine patients who refused EmC were followed up with expectant management. The mean gestational age at first examination was similar between the EmC (21.36±1.62 weeks) and control group (21.00±3.16 weeks, p=0.372). The median (range) volume of removed amniotic fluid was 151.82 (120-420) mL. Cases in the EmC group gained a significantly longer delay until delivery (47.72±28.14 days) compared to controls (2.33±0.5 days, p<0.001). All of the women in the control group gave birth within three days following admission to hospital. The mean gestational age at birth was significantly higher in the EmC group (28.18±4.53 weeks) than in the control group (21.57±3.53 weeks, p<0.001). Thirteen (59.09%) infants survived in the EmC group while only two infants (22.22%) of one patient survived in the control group (p<0.001).

Conclusion: EmC increases the survival rate of infants by prolonging the gestational age at delivery in twin pregnancies. Clinicians and patients should be encouraged regarding the use of EmC in twin pregnancies with a fully dilated cervix and prolapsed amniotic membranes. (J Turk Ger Gynecol Assoc. 2025; 26: 26-33)

Keywords: Twin pregnancies, fully dilated cervix, membrane prolapse, amnioreduction, emergency cervical cerclage

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Introduction

Twin pregnancy rates have increased markedly, mostly due to increased use of assisted reproductive technology and increasing maternal age and currently account for approximately 2-4% of total births worldwide (1). This significant increase has correlated with an increase in the preterm birth (PTB) frequency, as twin pregnancies have a 50% PTB rate, 12

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times greater PTB risk, and 5 times greater neonatal death risk than singleton pregnancies (2). It was reported that survival and survival without severe morbidity substantially improved with every additional week of pregnancy prolongation (3). Since PTB is the major reason for neonatal morbidity and mortality, despite significant advances in the area of neonatal intensive care, all possible measures should be considered to prevent PTB in twin gestations (4).

One of the main underlying mechanisms leading to spontaneous PTB in twins is acute cervical insufficiency (incompetency), defined as cervical dilatation without pain in the mid-trimester. This pregnancy complication is responsible for about 10-25% of all second-trimester pregnancy losses (5). The cervical insufficiency rate in cases with twins (5%) is significantly higher than among singleton cases (0.05-1.8%) (6). Cases frequently admitted to obstetric units with minimal symptoms, ending in a spontaneous cervical dilatation with membrane prolapse at or beyond the external cervical os. Also, direct contact of fetal membranes with vaginal flora could increase the risk of chorioamnionitis, and thus, extreme PTB (7). The total PTB rate in cervical insufficiency cases has been estimated to be nearly 90% (8). To decrease the adverse obstetric outcomes associated with PTB in twin pregnancies with acute cervical insufficiency, an optimal strategy for preventing PTB should be considered to prolong these pregnancies.

The use of therapeutic interventions, such as vaginal progesterone and tocolytics, in singleton pregnancies with dilated cervix was reported to decrease the PTB rate and neonatal morbidity and mortality (9,10). However, twin gestations did not exhibit as great a benefit from these treatment modalities as singletons (9,11). Cervical cerclage is a widely used method for prolonging the pregnancy duration in cases with cervical insufficiency. Two main types of this procedure are elective cerclage and emergency cerclage (EmC). Elective cerclage is usually performed at the end of the first trimester and indication is based on a history of a painless second-trimester delivery (12). EmC (rescue cerclage, physical examination-indicated cerclage), which refers to the placement of a cerclage in cases presenting with a painless cervical dilatation and prolapsed amniotic membranes towards the vagina, is a difficult method to conduct effectively (13). The main challenge in EmC is probably the elevated infection risk, because of the increased exposure of the amniotic membranes to vaginal bacteria, and it is hard to push the membranes back into the uterus against intrauterine pressure, especially in cases with a fully dilated cervix (14). Thus, the effectiveness and safety of this procedure remain controversial. Previous studies have demonstrated encouraging outcomes concerning the advantages of EmC in singleton pregnancies (15). However, data on the efficacy of dilated cervix-based cerclage in twin pregnancies are limited. Unlike singleton pregnancies, few studies have been conducted on the use of cerclage for dilated cervix in twin pregnancies with conflicting outcomes. Some of these investigations showed that EmC reduced the PTB and adverse neonatal outcome rates in twin pregnancies with dilated cervix (16). However, a recent study demonstrated that the neonatal outcomes of EmC had a more favorable prognosis in singleton pregnancies than in twin pregnancies, and twin pregnancy is an independent risk factor for PTB (17). Moreover, to the best of our knowledge, no study to date compares the efficacy of EmC and expectant management in twin pregnancies with fully dilated cervix and prolapsed membranes. Thus, there is little evidence to inform patient counseling about the risks and benefits of EmC placement in twin pregnancies. Thus, the capability to guide a patient with a twin pregnancy who is considered to be suitable for EmC is limited.

The aim of this study was to compare the outcomes of two groups of twin pregnancies with and without EmC and all with fully dilated cervix and prolapsed membranes. A secondary aim was to evaluate the effectiveness of EmC in these patients.

Material and Methods

This retrospective study included data on twin pregnancies with a fully dilated cervix and bulging intact fetal membranes presenting between December 2015 and December 2022. Cases included in this investigation were those with twin pregnancies who presented between 17 and 24 weeks of gestation with painless, fully dilated cervix diagnosed by physical examination and who delivered at the same hospital by the end of the pregnancy course. The study project was approved by the Institutional Ethics Committee of Dicle University Faculty of Medicine (approval number: 2021/322, date: 30.06.2021). The data were collected retrospectively from the patient files recorded during the examination, cerclage, antepartum, intrapartum, and postpartum periods. The patients were divided into two groups: the EmC group and the control group, consisting of women who refused cerclage (expectant management group). The results of both groups were compared. All patients were informed in detail about possible risks that may occur during and after the EmC procedure. Amnioreduction and EmC were performed only on patients who accepted the possible risks and gave their informed consent.

Exclusion criteria were: patients who had active uterine contractions; preterm premature amniotic membrane rupture; severe vaginal bleeding; history- or US-indicated cerclage placed earlier in the current pregnancy; clinical chorioamnionitis or placental abruption on presentation; intrauterine fetal demise or selective fetal reduction of one or more fetuses before

presentation; willingness for pregnancy termination; and pregnancies carrying fetuses with chromosomal or structural abnormalities detecting by US examination or other prenatal screening procedures. Furthermore, twin pregnancies that underwent cerclage due to cervical shortening or funneling, or prior history-indicated cerclage were not included in this study. Cases were excluded if EmC was performed after the delivery of one fetus of a twin pregnancy. We also excluded patients with missing medical records.

The fetuses and cervical structures of all patients were evaluated by an experienced clinician (A.Y.) with transabdominal and transvaginal ultrasound (Figure 1). Based on the patient's medical history for the current pregnancy, all patients underwent speculum and digital cervical examination several times prior to arrival. We avoided speculum and digital examination prior to EmC. Amnioreduction was performed in all patients before EmC. EmC was performed by the same surgeon (A.Y.), after all patients were evaluated clinically and had undergone laboratory investigations, including fever, leukocytosis, uterine contractions, bleeding, and premature rupture of membranes. We performed external tocodynamometry in all pregnant women before cerclage placement to eliminate PTB or impending miscarriage. EmC was not performed in cases considered to be in preterm labor following uterine activity monitoring. Tocolytics were not administered routinely preoperatively to all cases in the EmC group. After EmC, all cases received one of the following tocolytics: indomethacin, nifedipine, or progesterone. Moreover, one of these tocolytics was administered to all cases in the control group. All cases in the EmC group received broad-spectrum antibiotics perioperatively. These cases were hospitalized following the EmC procedure for 10-14 days and then discharged with close outpatient follow-up if the transvaginal US showed a closed cervix. Parenteral antibiotic and vaginal iodine treatment were continued in the hospital for 10-14 days in patients in the EmC group whose pregnancy was still ongoing. The regimens and duration of use were determined based on the discretion of the attending surgeon. Antenatal corticosteroid treatment was administered, based on the gestational age at presentation and outcomes of the EmC. Abstinence from sexual intercourse was recommended and the patients were advised to avoid challenging physical effort. Bed rest was not routinely advised. The patients in the control group were followed up as inpatients and received tocolytic drugs, parenteral antibiotics, antenatal corticosteroids (at 23-24 weeks of pregnancy), and bed rest until delivery.

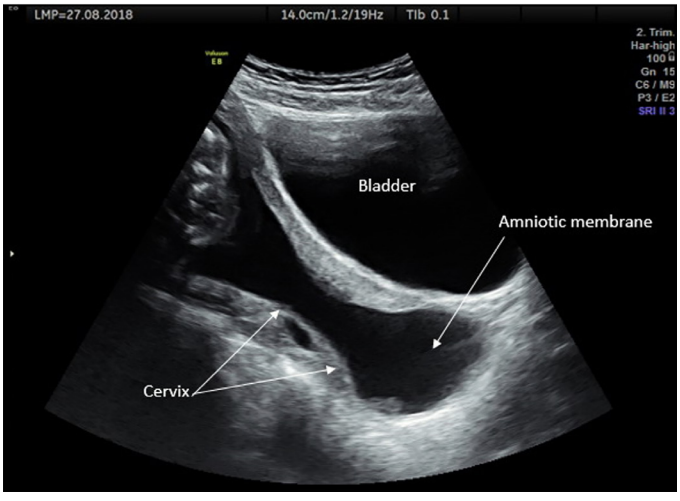

Figure 1. Transabdominal ultrasound image of a patient presented with a fully dilated cervix and amniotic membrane prolapse

Demographic, clinical features and treatment approaches of both groups were evaluated in detail. The mean gestational age of both groups during the first admission and delivery, the occurrence of clinical chorioamnionitis, fetal survival, time from EmC to delivery, mean birth weight, neonatal intensive care unit (NICU) admission, and postnatal survival were evaluated. Data regarding pregnancy and neonatal outcomes in cases delivered at another hospital were collected by phone contact with families directly or with the treating clinicians of the hospitals.

Clinical chorioamnionitis was diagnosed by the presence of maternal fever (≥38 ºC orally) with no evidence of an extrauterine cause related to at least two of the following signs: abdominal pain, uterine tenderness, maternal tachycardia (>100 beats/minute), fetal tachycardia (>160 beats/minute), leukocytosis, and new-onset purulent foul-smelling vaginal discharge (18).

Technical details of EmC

1. Amnioreduction: Amnioreduction was conducted under transabdominal ultrasound guidance with a 20-gauge needle at different positions on the ventral aspect of the uterus. Amnioreduction facilitates the repulsion of amniotic membranes and reduces tension on the fetal membranes and the risk of membrane rupture. Thus, amnioreduction provides retraction before cerclage placement and allows preservation of the borders of the cervix (19). The volume of amniotic fluid reduction was determined according to the distension of the bulging sac, ranging from 120 to 420 mL (20). Amnioreduction proceeded until the prolapsed membranes showed a deflated appearance.

2. Surgical technique:

- Under general or spinal anesthesia and after cleaning the perineum, the vagina is gently explored with Breisky retractors in the Trendelenburg position.

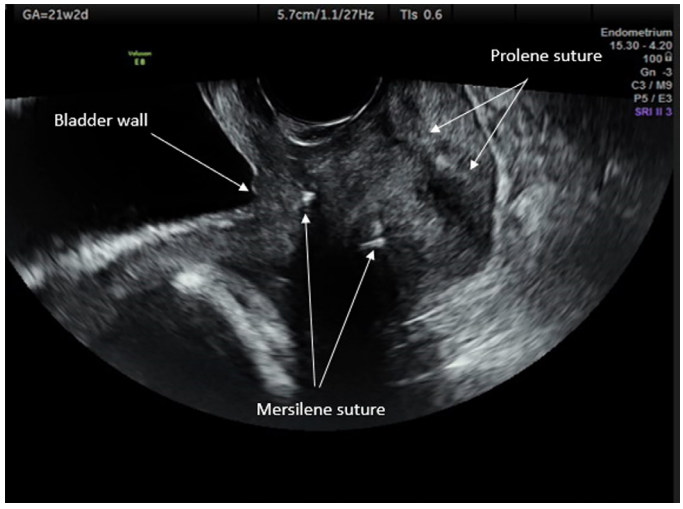

Figure 2. Transabdominal ultrasound image of a patient following emergency cervical cerclage

- After cleaning the vagina with plenty of iodine, the cervix is pulled up by holding with forceps.
- Light pressure is applied to the lower outer cervical wall with the Breisky retractor tip and the pouch is gently pushed back with a finger.
- When the pouch is fully retracted, the entire cervix is grasped with ovarian forceps, and the membranes are prevented from protruding.
- Double suture technique: The proximal cervix is sutured as high as possible with polyester fiber ligature (Ethicon Mersilene Tape® RS22 5 mm x 40 cm). Care should be taken to avoid penetrating the ureters. The open distal cervix is sutured with a polypropylene (Prolene Ethicon®) suture (Figure 2).

Statistical analysis

SPSS, version 22.0, was used for analyzing the clinical data (IBM Inc., Armonk, NY, USA). Descriptive statistics are summarized as counts and percentages for categorical variables, and mean ± standard deviation and range (minimum-maximum) for continuous variables. A Kolmogorov-Smirnov test was performed to determine whether or not parameters were normally distributed. Continuous variables were compared using either the Student's t-test or the Mann-Whitney U test among the groups, as appropriate. Differences in categorical variables between groups were evaluated using Fisher's exact test. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 20 patients with fully dilated cervix and bulging intact fetal membranes were included. Eleven patients who underwent EmC after amnioreduction were included in the study group and nine patients who were followed up with expectant management were included in the control group.

The type of pregnancy, the volume of amniotic fluid reduction, mode of delivery, and neonatal survival in both groups are presented in Table 1. On examination of pregnancy history, none of the patients in the EmC group had any surviving children. Three of eleven (27.3%) conceived spontaneously and the other eight conceived through ovulation induction protocols or IVF treatment. Five patients in the control group had previously surviving children and eight of nine (88.9%) conceived spontaneously.

Demographic and clinical characteristics and pregnancy outcomes of both groups are presented in Table 2. The mean maternal age did not differ between the EmC group (26.90±6.12 years) and the control group (27.55±5.65 years, p=0.405). The mean number of gravida and previous abortions were also similar in the EmC and control groups (2.54±1.69 vs. 2.66±1.80, p=0.439 and 1.18±1.53 vs. 0.44±1.01, p=0.342 respectively). The mean gestational age at the first examination was similar between the EmC group (21.36±1.62 weeks) and the control group (21.00±3.16 weeks, p=0.372). The median (range) amount of removed amniotic fluid was 151.82 (120-420 mL). No cases experienced intraoperative membrane rupture in the EmC group. Cases in the EmC group gained a significantly longer interval time to delivery (47.72±28.14 days) compared to pregnant women in the expectant management group (2.33±0.5 days, p<0.001). When the surviving neonates in both of the groups were compared, the mean interval time to delivery was prolonged by 64 days the EmC group, while the mean interval time to delivery was prolonged by only two days in surviving neonates in the control group (p<0.001). All of the pregnant women in the control group gave birth within three days of admission to hospital. The mean gestational age at birth was significantly higher in the EmC group (28.18±4.53 weeks) than in the control group (21.57±3.53 weeks, p<0.001). Furthermore, the mean gestational age at delivery of the surviving fetuses differed between the two groups, with EmC cases delivering at a mean of 30.57±3.82 weeks, compared with cases managed expectantly which were delivered at 25 weeks (p<0.001).

All pregnant women in the EmC group were delivered due to the preterm onset of active uterine contractions. Nine (81.81%) of the patients in the EmC group were delivered by Cesarean section. The survival rates were significantly different between the two groups (p<0.001) with 13 (59.09%) babies in the EmC group surviving, including one with cerebral palsy (CP) while in the control group, the twin babies of only one patient (11.11%) survived. The mean overall birth weight in the EmC group was 1264±70 grams and in the 13 surviving neonates it was 1640±509 grams. In cases treated with expectant

Table 1. Type of pregnancy, the volume of amniotic fluid reduction, mode of delivery, and neonatal survival in both groups

Groups	Pregnancy type	Amnioreduction (mL)		Delivery type	Neonatal survival	
		Fetus 1	Fetus 2		Fetus 1	Fetus 2
EmC group, (n=11)	In vitro fertilization	180	0	Cesarean	Healthy	Healthy
	In vitro fertilization	140	140	Cesarean	Healthy	Healthy
	Spontaneous	140	100	Cesarean	Healthy	Cerebral palsy
	Spontaneous	140	0	Vaginal	Demise	Demise
	Ovulation induction	140	120	Cesarean	Healthy	Healthy
	In vitro fertilization	160	0	Vaginal	Demise	Demise
	In vitro fertilization	180	120	Cesarean	Demise	Demise
	Ovulation induction	160	100	Cesarean	Healthy	Demise
	In vitro fertilization	420	140	Cesarean	Demise	Demise
	Spontaneous	240	0	Cesarean	Healthy	Healthy
	In vitro fertilization	400	320	Cesarean	Healthy	Healthy
Control group, (n=9)	In vitro fertilization	-	-	Cesarean	Healthy	Healthy
	Spontaneous	-	-	Vaginal	Demise	Demise
	Spontaneous	-	-	Cesarean	Demise	Demise
	Spontaneous	-	-	Cesarean	Demise	Demise
	Spontaneous	-	-	Abortion	Demise	Demise
	Spontaneous	-	-	Abortion	Demise	Demise
	Spontaneous	-	-	Abortion	Demise	Demise
	Spontaneous	-	-	Abortion	Demise	Demise
	Spontaneous	-	-	Abortion	Demise	Demise

Table 2. Demographic and clinical characteristics and results of both groups

	Emergency cerclage group (n=11)		Control group (n=9)		p
	Mean ± SD	Range	Mean ± SD	Range	
Maternal age, years	26.90±6.12	18-38	27.55±5.65	18-37	0.404
Gravida, (n)	2.54±1.69	1-5	2.66±1.80	1-6	0.439
Parity, (n)	0.36±1.15	0-4	1.22±1.64	0-5	0.098
Previous abortion, (n)	1.18±1.53	0-4	0.44±1.01	0-3	0.342
Previous term delivery, (n)	-	-	1.22±1.64	0-5	-
Gestational age at presentation, weeks	21.36±1.62	19-24	21.00±3.16	17-24	0.372
Gestational age at birth, weeks (all fetuses)	28.18±4.53	22-34	21.57±3.53	17-24	**<0.001**
Gestational age at birth, weeks (survivors)	30.57±3.82	23-34	25	25	**<0.001**
Prolonged gestational age (all fetuses), days	47.72±28.14	7-91	2.33±0.5	2-3	**<0.001**
Prolonged gestational age (survivors), days	64.0±20.38	28-91	2	2	**<0.001**
Birth weight (all fetuses), (g)	1264±70	450-2400	573±12	380-700	**0.008**
Birth weight (survivors), (g)	1640±509	660-2400	648±24	630-665	**<0.001**
NICU admission of the surviving neonates	13 (100%)		2 (100%)		1.000
Number of babies surviving	13 (59.09%)		2 (11.11%)		**0.001**
SD: Standard deviation, NICU: Neonatal intensive care unit					

management, the mean weight of four individual twins was 573 grams (excluding five miscarriages), and the two surviving babies were 630 and 665 grams. The 1 min Apgar score of the surviving neonates in the EmC group ranged between 2 and 8, and the 5 min Apgar score between 4 and 9. The 1 min and 5 min Apgar scores of the surviving babies in the control group were 4-7 (fetus 1) and 5-7 (fetus 2), respectively. All surviving neonates required NICU admission in both of the groups.

None of the cases who underwent EmC with amnioreduction suffered from complications, including preterm premature membrane rupture, clinical chorioamnionitis or other adverse outcomes associated with amniocentesis. Moreover, no cases in the control group experienced clinical chorioamnionitis.

Discussion

In the current study, 11 cases with twin pregnancies who experienced EmC for a painless fully dilated cervix are included and their features at presentation and pregnancy outcomes after the EmC procedure are described. These features and pregnancy outcomes were compared with patients with twin pregnancies with a fully dilated cervix who experienced expectant management. The findings show that the use of EmC in twin pregnancies with fully dilated cervix was related to a significantly longer interval from presentation to delivery compared with expectant management. All cases managed expectantly gave birth within three days, starkly underlining the unfavorable prognosis in the absence of intervention. Thus, the mean gestational week at delivery was significantly higher in the EmC group than in the expectantly managed group. Furthermore, the rate of neonatal survival to discharge was substantially higher in the EmC group compared with the control group. To the best of our knowledge, this is the first cohort study comparing the efficacy of EmC and expectant management in twin pregnancies with fully dilated cervix and prolapsed membranes. Our clinical protocol is to routinely recommend an EmC procedure to twin pregnancies with painless fully dilated cervix in the second trimester.

This study included only twin pregnancies with fully dilated cervix and prolapsed membranes. Pelvic discomfort and vaginal discharge should be questioned at every ultrasound examination in all twin pregnancies. If there is a complaint, cervical length, funneling and softness should be evaluated by transvaginal sonography.

There are a few articles in the literature about singleton pregnancies undergoing EmC after amnioreduction. In a retrospective cohort study on cerclage vs. expectant management of twin pregnancies with ≥1 cm cervical dilatation, Roman et al. (16) stated that although the cerclage results are promising, more studies are needed. In a meta-analysis, three randomized controlled trials included twin pregnancies with a cervical length <2.5 cm, screened by transvaginal ultrasound before 24 weeks of gestation. A total of 49 twins with a short cervical length were identified with 24 in the cerclage group and 25 in the control group. The key message of this meta-analysis is that cerclage does not prevent PTB in asymptomatic twin gestations with a maternal short cervical length measured by transvaginal ultrasound (21). In a study conducted in Denmark, cerclage was applied to 65 twin pregnant women with emergency and ultrasound indications. Pregnancy was prolonged by 48 days in the 18 patients group with emergency cerclage indication and by 81 days in the 47 patients group with ultrasound cerclage indication (22). In another study, EmC was applied to 12 multiply pregnant (10 twins and 2 triplets) women with visible fetal membranes through a dilated internal cervical os on speculum examination. These authors concluded that emergency cerclage placement was associated with a pregnancy prolongation of 60.25 days and a presumed parallel benefit of increased neonatal survival and higher birth weight (23). A retrospective cohort study in dichorionic diamniotic twin gestations with short cervix has shown that cervical cerclage was associated with a 60% reduction in the rate of spontaneous birth <32 weeks gestation (24). We suggest that EmC may be more effective than any other method in patients with complete cervical dilatation and membrane prolapse. Gestational week went from around 21 weeks in the EmC group to approximately 28 weeks in all cases in the EmC group and was over 30 weeks in surviving cases in this group, whereas the gestational age was prolonged by only 2.3 days in the non-cerclage group. It is not possible to find published randomized controlled studies, there are only case reports in which EmC was applied following amnioreduction. In a series of eight singleton cases who underwent EmC after amnioreduction, a median of 132.9 (60-230) mL amniotic fluid was removed and the mean gestational age was prolonged by 27.1 days and four live infants were delivered (25). In the present study, the median volume of removed amniotic fluid was 151.82 mL and the mean gestational age was prolonged by approximately 48 days in the EmC group compared to only 2.3 days in the control group. Of note, in the seven pregnancies with surviving newborns from the EmC group, pregnancy was prolonged by approximately 64 days. We hope that our results will encourage the concerned obstetricians, especially in patients with a strong desire to have children, that EmC may be used in consenting, fully-informed patients.

Pregnant women who present with cervical dilation of ≥4 cm may experience poorer pregnancy outcomes following EmC. When cervical dilation reaches ≥4 cm, the membranes bulging beyond the cervix increase their level of distension (26). In addition, repeatedly manipulating the membranes during surgery can further raise this distension, heightening

the risk of rupture. The primary goal of amnioreduction is to alleviate membrane distension. Following amnioreduction, membrane distension is significantly decreased, which in turn simplified the procedure and reduced operation time (25). Our findings indicate that amnioreduction can effectively improve pregnancy and delivery outcomes in patients with significant cervical dilation, aligning with previous research.

In the present study, all cases in the EmC group received parenteral prophylactic antibiotics and vaginal iodine therapy for 10-14 days. Also, anti-contraction medications were used in both groups and all were advised bed rest. Given our findings, it appears that these treatments alone were not effective, unless cerclage was also applied. Due to the parenteral and local treatment, no signs of systemic infection were found in any of the patients. We believe that the addition of vaginal iodine treatment during parenteral treatment is effective in preventing ascending infection.

In a systematic review on PTB prevention in twin pregnancies, the use of vaginal progesterone in twin pregnancies was shown to reduce preterm labor and improve newborn outcomes. It was concluded that there were very limited data on cerclage and further research was required to reduce the risks of PTB and its sequelae in twin pregnancies, including the use of combinations of therapies (27). The risk of PTB is high in multiple pregnancies and it is much more difficult to prevent PTB in these patients compared to singleton pregnancies. Demonstrably effective interventions for the prevention of PTB in twin gestations are lacking. In the present study, most of the patients used progesterone during their pregnancies, and bed rest is commonly advised in patients who become pregnant with infertility treatment, but PTB was not prevented by progesterone. In the present study, PTB was irreversible, and some patients were treated with “heroic cerclage” to give them a chance. Despite the worse obstetric history in the EmC cases, much better results were obtained with high-level EmC compared to the control group. No serious infection was detected in any of the patients clinically in the postoperative period. In one twin, a younger sibling was diagnosed with CP in the late postoperative period.

The main strength of this study is that, to the best of our knowledge, this is the first cohort study to demonstrate the efficacy of EmC in twin pregnancies with a fully dilated cervix. All cases in the EmC group were evaluated and informed by a single perinatologist, EmC was performed by an experienced surgical team and followed up by the same team after surgery.

Study limitations

However, there are some limitations. A lack of detailed information on patient management before hospital presentation introduces a potential confounding factor, which could affect the accuracy of the study's outcomes. Moreover, the retrospective nature of this study may introduce bias to the findings. The relatively small sample size also increases the risk of bias and also limits the generalizability of the findings, making it difficult to draw strong conclusions applicable to the wider population. Finally, variability in patient choices introduced a level of selection bias that could affect the comparability between the EmC and control groups.

Conclusion

Although the obstetric history of the EmC group was worse than that of the control group, a significantly higher proportion of neonates survived compared with the expectant management group (59% vs. 11%). Moreover, EmC prolonged the gestational age at delivery, thus, increasing the babies’ chances of survival. However, given the limitations of our study, more prospective randomized controlled studies are needed.

Ethics

Ethics Committee Approval: *The study project was approved by the Institutional Ethics Committee of Dicle University Faculty of Medicine (approval number: 2021/322, date: 30.06.2021).*

Informed Consent: *Amnioreduction and EmC were performed only on patients who accepted the possible risks and gave their informed consent.*

Footnotes

Author Contributions: *Surgical and Medical Practices: A.Y., Concept: A.Y., S.C.O., R.G., E.Z.Y., G.B., M.Y., Design: A.Y., S.C.O., R.G., M.Y., Data Collection or Processing: A.Y., R.G., Analysis or Interpretation: A.Y., S.C.O., Literature Search: A.Y., S.C.O., E.Z.Y., G.B., Writing: A.Y., S.C.O., Critical review: S.C.O.*

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Preoperative predictors of concurrent endometrial carcinoma in patients with endometrial intraepithelial neoplasia: the role of HALP score and other inflammatory markers

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Abstract

Objective: The aim of this study was to identify preoperative factors that predict concurrent endometrial carcinoma in patients with endometrial intraepithelial neoplasia (EIN), focusing on inflammatory markers, such as hemoglobin, albumin, lymphocyte, and platelet (HALP) score, prognostic nutritional index (PNI), the modified systemic inflammatory score (mSIS), clinical characteristics, and imaging findings.

Material and Methods: A retrospective review was conducted of patients diagnosed with EIN who underwent hysterectomy and bilateral salpingo-oophorectomy between 2019 and 2024. Data collected included demographic details, cancer antigen-125 levels, hematological parameters, HALP score, PNI, mSIS, and preoperative endometrial thickness. Statistical analyses were performed to evaluate the associations between these factors and concurrent endometrial carcinoma.

Results: Concurrent endometrial carcinoma was identified in 39 (19.9%) of the total of 196 patients included. Significant predictors included older age ($p<0.001$), lower platelet count ($p<0.001$), and endometrial thickness greater than 13 mm ($p=0.044$). Inflammatory markers such as the HALP score, PNI, and mSIS did not show significant associations. The majority of cases with carcinoma were International Federation of Gynecology and Obstetrics stage IA (76.9%) and grade 1 endometrioid tumors (94.9%).

Conclusion: Advanced age, reduced platelet count, and increased endometrial thickness are key predictors of concurrent endometrial carcinoma in patients with EIN. These findings may be useful for improved preoperative risk stratification and inform surgical planning. Further research is needed to explore the role of inflammatory biomarkers in this context. (J Turk Ger Gynecol Assoc. 2025; 26: 34-40)

Keywords: Endometrial intraepithelial neoplasia, endometrial carcinoma, HALP score, Inflammatory markers, preoperative predictors

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Introduction

Endometrial intraepithelial neoplasia (EIN) is recognized as a precursor lesion that significantly increases the risk for the development of endometrioid endometrial carcinoma. Histopathological overlap between EIN and endometrial cancer is not uncommon, with studies reporting that up to 40% of patients diagnosed with EIN may harbor concurrent endometrial carcinoma at the time of hysterectomy (1-3). Several risk factors for the development of EIN and its

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progression to cancer have been identified, including metabolic conditions linked to prolonged unopposed estrogen exposure, leading to precancerous endometrial alterations (4).

The potential relationship between inflammation and cancer was first highlighted by Balkwill and Mantovani (5) in the 19th century, who suggested that chronic inflammation might contribute to tumorigenesis. Recent studies have demonstrated that systemic inflammation plays a critical role in the development and progression of some cancers, influencing both tumor growth and patient outcomes (6). Several serum-based inflammatory biomarkers, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and more complex indices like the modified systemic inflammatory score (mSIS), prognostic nutritional index (PNI), and hemoglobin, albumin, lymphocyte, and platelet (HALP) score, have been investigated for their prognostic value across various malignancies (7-12). There are studies showing that high NLR is associated with poorer prognosis in patients with endometrial cancer (13), and studies reporting that both NLR and PLR are important predictors of prognosis in ovarian cancer (14). Similarly, emerging indices, such as HALP score and PNI have been evaluated in cervical cancer (15,16).

In the present study, the aim was to evaluate whether preoperative factors, including patient demographics, imaging findings, and laboratory parameters, and in particular a range of inflammatory markers, could serve as predictors of concurrent endometrial carcinoma in patients diagnosed with EIN who underwent hysterectomy. It is hoped that this may help refine preoperative risk stratification and guide surgical decision-making.

Material and Methods

This retrospective study analyzed patients diagnosed with EIN who underwent hysterectomy and bilateral salpingo-oophorectomy between 2019 and 2024. Data were obtained from electronic medical records, patient files, and pathology reports. Patients who had undergone fertility-sparing management following an EIN diagnosis were excluded from the study. Furthermore, individuals with concurrent endometrial malignancy identified during endometrial sampling were also excluded. This study was approved by the Ethics Committee of Ankara Bilkent City Hospital (approval number: TABED 1-24-157, date: 24.04.2024).

The collected data included demographic information, cancer antigen-125 (CA-125) levels, hematological parameters, calculated HALP score, PNI, and mSIS, and ultrasound findings in particular endometrial thickness, together with final definitive pathology results. Hematological parameters such as serum albumin, hemoglobin, platelet, lymphocyte, monocyte, and neutrophil counts were recorded preoperatively. The HALP score was calculated using the formula; hemoglobin (g/L) × albumin (g/L) × lymphocyte (10^9/L)/platelet (10^9/L) (17). PNI was determined using the formula: [10 × albumin (g/L) + 0.005 × total lymphocyte count] (12). The mSIS was defined as follows: patients with an albumin level <40 g/L and lymphocyte-to-monocyte ratio (LMR) <4.44 were assigned a score of 2; those with either an albumin level ≥40 g/L or LMR ≥4.44 were assigned a score of 1; and in patients with both an albumin level ≥40 g/L and LMR ≥4.44 the assigned score was 0 (18).

Frozen/section analysis was routinely performed on all EIN patients. Patients who met one of the following criteria underwent routine pelvic and para-aortic lymphadenectomy: grade 1 or 2 endometrioid adenocarcinoma with a tumor size ≥2 cm, >50% myometrial invasion, all grade 3 endometrioid adenocarcinomas, extrauterine metastasis, cervical involvement, and any non-endometrioid adenocarcinomas. Staging was carried out based on the revised 2009 International Federation of Gynecology and Obstetrics (FIGO) criteria (19).

Statistical analysis

Statistical analysis was performed using IBM SPSS, version 22.0 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed as mean ± standard deviation or median (range) for continuous variables and as number (percentage) for categorical variables. The chi-square test was used to assess categorical variables. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 196 patients diagnosed with EIN based on endometrial sampling were included in this study. The mean age of the patients was 51.4±9.5 years, ranging 31-83 years. The median preoperative values for CA-125, albumin, hemoglobin, platelet count, lymphocytes, monocytes, and neutrophils were 10.9 IU/mL, 45.5 g/L, 12.8 g/dL, 291x10^9/L, 2x10^9/L, 0.4x10^9/L, and 4.5x10^9/L, respectively. The mean NLR was 2.5±1.2, MLR was 0.2±0.2, PLR was 153.8±56.2, HALP score was 43.3±21.9, and PNI was 46.2±3.4. The mean preoperative endometrial thickness was 11±5.8 mm. The mSIS was 0 in 170 patients (86.7%) and 1 in 26 patients (13.3%). Final pathology results showed that 39 patients (19.9%) had concurrent endometrial cancer. The clinical characteristics and pathological outcomes of the patients are detailed in Table 1.

The pathological characteristics of the 39 patients with concurrent endometrial cancer are presented in Table 2. The most common FIGO stage was IA, which was found in 30 (76.9%). All patients had endometrioid-type tumors, with 37 (94.9%) being classified as FIGO grade 1. Twelve (30.8%) had

Table 1. Clinical characteristics of the patients (n=196 patients)

Features		Mean ± SD	Median (range)
Age (years)		51.4±9.5	50 (31-83)
CA-125 (IU/mL)		16.3±26.1	10.9 (2-213)
Albumin (g/L)		45.2±3.4	45.5 (28-52)
Hemoglobin (g/dL)		12.8±1.6	12.9 (6.3-16.6)
Platelet (10^9/L)		300±80	291 (127-538)
Lymphocyte (10^9/L)		2.2±1.1	2 (0.6-14.1)
Monocyte (10^9/L)		0.4±0.4	0.4 (0.2-5.8)
Neutrophil (10^9/L)		4.9±1.9	4.5 (0.3-12.6)
Neutrophil-to-lymphocyte ratio		2.5±1.2	2.2 (0.1-8.7)
Monocyte-to-lymphocyte ratio		0.2±0.2	0.2 (0.03-2.1)
Platelet-to-lymphocyte ratio		153.8±56.2	142.7 (21-422)
HALP score[1]		43.3±21.9	40.4 (11-243)
PNI[2]		46.2±3.4	46.5 (28.3-53.3)
Endometrial thickness (mm)[3]		11±5.8	10.5 (1-35)
		n	**%**
mSIS[4]	0	170	86.7
	1	26	13.3
	2	0	0
Final pathology	EIN	157	80.1
	Cancer	39	19.9
Ovarian pathology	Benign	195	99.5
	Cancer[5]	1	0.5

[1]: HALP: Hemoglobin (g/L) x albumin (g/L) x lymphocyte (n/L)/platelet (n/L), [2]: PNI: Prognostic nutritional index, [3]: (n=170) patients (endometrial thickness value was not reported in 26 patients), [4]: mSIS: Modified systemic inflammatory score, [5]: Adult granulosa cell tumor, SD: Standard deviation, CA-125: Cancer antigen-125

Table 2. Pathologic features of patients with endometrial cancer (n=39)

Pathologic characteristics		n	%
FIGO 2009 stage	IA	30	76.9
	IB	6	15.4
	II	2	5.1
	IIIC2	1	2.6
FIGO grade	Endometrioid grade 1	37	94.9
	Endometrioid grade 2	1	2.6
	Endometrioid grade 3	1	2.6
Depth of myometrial invasion	No invasion	12	30.8
	<1/2	18	46.2
	≥1/21	8	4.1
	Serosal invasion	1	0.5
Lymphovascular space invasion	Negative	34	87.2
	Positive	5	12.8
Cervical invasion	Negative	35	89.7
	Glandular invasion	1	2.6
	Stromal ± glandular invasion	3	7.7
Peritoneal cytology	Negative	39	100
	Positive	0	0
Lymphadenectomy	Not performed	30	76.9
	Performed	9	23.1

FIGO: International Federation of Gynecology and Obstetrics, [1]: Except serosal invasion

no myometrial invasion, while 1 (0.5%) had serosal invasion. Lymphovascular space invasion was present in 5 (12.8%), and cervical stromal and/or glandular invasion was noted in 3 (7.7%).

Table 3 presents the relationship between preoperative clinical factors and inflammatory markers and the presence of concurrent endometrial cancer. A significant relationship was found between higher age, lower platelet counts and the presence of concurrent endometrial carcinoma. A significant correlation (p=0.044) was identified between an endometrial thickness exceeding 13 mm and the presence of concurrent endometrial cancer, with a sensitivity of 42.4%, specificity of 75.2%, positive predictive value of 29.2%, and negative predictive value of 24.4% (Table 4).

Discussion

The aim of the present study was to evaluate predictive factors for concurrent endometrial carcinoma in patients diagnosed with EIN undergoing hysterectomy. Among 196 patients included in the study, 19.9% were found to have concurrent endometrial

Table 3. Association of preoperative clinical variables and inflammatory markers with concurrent endometrial cancer

Factor		EIN	Cancer	Sensitivity, (%)	Specificity, (%)	PPV, (%)	NPV, (%)	p
		n (%)	n (%)					
Age (years)[1]	≤50	97 (89.8)	11 (10.2)	71.8	61.8	31.8	89.8	**<0.001**
	>50	60 (68.2)	28 (31.8)					
CA-125 (IU/mL)[1]	≤10.9	83 (82.2)	18 (17.8)	53.8	52.9	22.1	82.2	0.453
	>10.9	74 (77.9)	21 (22.1)					
Albumin (g/L)[1]	>45.5	80 (81.6)	18 (18.4)	53.8	51.0	21.4	81.6	0.591
	≤45.5	77 (78.6)	21 (21.4)					
Hemoglobin (g/dL)[1]	>12.9	77 (80.2)	19 (19.8)	51.3	49.0	20.0	80.2	0.971
	≤12.9	80 (80.0)	20 (20.0)					
Platelet (10^9/L)[1]	>291	89 (90.8)	9 (9.2)	76.9	56.7	30.6	90.8	**<0.001**
	≤291	68 (69.4)	30 (30.6)					
Lymphocyte (10^9/L)[1]	≤2	77 (76.2)	24 (23.8)	38.5	49.0	15.8	76.2	0.162
	>2	80 (84.2)	15 (15.8)					
Monocyte (10^9/L)[1]	≤0.4	100 (83.3)	20 (16.7)	48.7	63.7	25.0	83.3	0.154
	>0.4	57 (75.0)	19 (25.0)					
Neutrophil (10^9/L)[1]	≤4.5	79 (79.0)	21 (21.0)	46.2	50.3	18.8	79.0	0.693
	>4.5	78 (81.3)	18 (18.8)					
Neutrophil-to-lymphocyte ratio[1]	≤2.2	78 (83.0)	16 (17.0)	59.0	49.7	22.5	83.0	0.333
	>2.2	79 (77.5)	23 (22.5)					
Monocyte-to-lymphocyte ratio[1]	≤0.2	100 (82.6)	21 (17.4)	46.2	63.7	24.0	82.6	0.257
	>0.2	57 (76.0)	18 (24.0)					
Platelet-to-lymphocyte ratio[1]	≤142.7	78 (78.8)	21 (21.2)	46.2	49.7	18.6	78.8	0.642
	>142.7	79 (81.4)	18 (18.6)					
HALP score[1,2]	>40.4	76 (77.6)	22 (22.4)	43.6	48.4	17.3	77.6	0.371
	≤40.4	81 (82.7)	17 (17.3)					
PNI[1,3]	>46.5	82 (82.8)	17 (17.2)	56.4	52.2	22.7	82.8	0.334
	≤46.5	75 (77.3)	22 (22.7)					
Endometrial thickness (mm)[1,4]	≤10.5	68 (80.0)	17 (20.0)	48.5	49.6	18.8	80.0	0.846
	>10.5	69 (81.2)	16 (18.8)					
mSIS[1,5]	0	138 (81.2)	32 (18.8)	17.9	87.9	26.9	81.2	0.335
	1	19 (73.1)	7 (26.9)					

[1]: Median value, [2]: HALP: Hemoglobin (g/L) x albumin (g/L) x lymphocyte (n/L)/platelet (n/L), [3]: PNI: Prognostic nutritional index, [4]: (n=170) patients (endometrial thickness value wasn't reported in 26 patients), [5]: mSIS: Modified systemic inflammatory score, EIN: Endometrial intraepithelial neoplasia, PPV: Positive predictive value, NPV: Negative predictive value

Table 4. Association of endometrial thickness with concurrent endometrial cancer

Endometrial thickness[1]	EIN	Cancer	Sensitivity, (%)	Specificity, (%)	PPV, (%)	NPV, (%)	p
	n (%)	n (%)					
≤3 mm	9 (75.0)	3 (25.0)	90.9	6.6	19.0	75.0	0.612
>3 mm	128 (81.0)	30 (19.0)					
≤4 mm	13 (68.4)	6 (31.6)	81.8	9.5	17.9	68.4	0.155
>4 mm	124 (82.1)	27 (17.9)					
≤5 mm	21 (75.0)	7 (25.0)	78.8	15.3	18.3	75.0	0.413
>5 mm	116 (81.7)	26 (18.3)					
≤6 mm	25 (73.5)	9 (26.5)	72.7	18.2	17.6	73.5	0.245
>6 mm	112 (82.4)	24 (17.6)					
≤7 mm	36 (78.3)	10 (21.7)	69.7	26.3	18.5	78.3	0.640
>7 mm	101 (81.5)	23 (18.5)					
≤8 mm	50 (78.1)	14 (21.9)	57.6	36.5	17.9	78.1	0.528
>8 mm	87 (82.1)	19 (17.9)					
≤9 mm	58 (79.5)	15 (20.5)	54.5	42.3	18.6	79.5	0.745
>9 mm	79 (81.4)	18 (18.6)					
≤10 mm	68 (80.0)	17 (20.0)	48.5	49.6	18.8	80.0	0.846
>10 mm	69 (81.2)	16 (18.8)					
≤11 mm	78 (81.3)	18 (18.8)	45.5	56.9	20.3	81.3	0.804
>11 mm	59 (79.7)	15 (20.3)					
≤12 mm	90 (83.3)	18 (16.7)	45.5	65.7	24.2	83.3	0.232
>12 mm	47 (75.8)	15 (24.2)					
≤13 mm	103 (84.4)	19 (15.6)	42.4	75.2	29.2	84.4	**0.044**
>13 mm	34 (70.8)	14 (29.2)					

[1]: (n=170) patients (endometrial thickness value was not reported in 26 patients), EIN: Endometrial intraepithelial neoplasia, PPV: Positive predictive value, NPV: Negative predictive value

carcinoma based on final pathology results. This is consistent with previous studies that report concurrent carcinoma rates ranging from 20% to 40% in patients with EIN, underscoring the significant overlap between EIN and endometrial cancer (1,20).

A key finding of our study was the association between higher age and the presence of concurrent endometrial carcinoma. This result is consistent with prior studies, which highlights increasing age as a significant risk factor for endometrial hyperplasia progression and cancer development (21). Aging is associated with prolonged exposure to unopposed estrogen, as well as age-related alterations in immune and inflammatory responses, which may further predispose patients to carcinogenesis. In the study conducted by Giannella et al. (22), and similar to our findings, patients with concurrent cancer were older.

Endometrial thickness, as measured preoperatively on ultrasound, was also found to be significantly associated with concurrent endometrial carcinoma, particularly for values exceeding 13 mm in our cohort. This finding confirms previous studies that have identified increased endometrial thickness as a predictor of malignancy in patients with EIN (23,24). However, the sensitivity and specificity of this cut-off remain suboptimal (42.4% and 75.2%, respectively), highlighting the need for multimodal risk assessment strategies that include clinical, radiological, and laboratory parameters.

Inflammatory biomarkers, including the HALP score, PNI, and mSIS were also evaluated. Although these indices have been shown to predict prognosis and recurrence in various malignancies (9,25-29), they did not reach statistical significance in predicting concurrent endometrial carcinoma in the present study. This may be attributed to the early-stage nature of the disease in most patients or the relatively small sample size, or both. However, given their availability in other malignancies, future studies with larger cohorts are needed to validate their predictive value in patients with EIN.

The current study also identified an association between lower platelet counts and concurrent endometrial carcinoma in patients with EIN. While the underlying mechanism remains unclear, this finding may reflect alterations in the inflammatory or hematopoietic environment associated with malignancy. Further studies are needed to explore this relationship.

Study Limitations

The strengths of our study include the relatively large sample size and comprehensive evaluation of preoperative factors, including inflammatory biomarkers, hematological parameters, and imaging findings. However, certain limitations should be acknowledged. First, the retrospective nature of the study introduces potential selection and information biases. Second, the sample size, while sufficient for preliminary analysis, may limit the power to detect associations between inflammatory markers and concurrent carcinoma.

Conclusion

The present study found and confirmed earlier results that older age, lower platelet counts, and endometrial thickness greater than 13 mm were significant predictors of concurrent endometrial carcinoma in patients with EIN undergoing hysterectomy. It is hoped that these findings can aid in refining preoperative risk stratification and surgical decision-making. Further, larger prospective studies are needed to validate the role of systemic inflammatory biomarkers and other preoperative factors in predicting concurrent malignancy in this patient population.

Ethics

Ethics Committee Approval: *This study was approved by the Ethics Committee of Ankara Bilkent City Hospital (approval number: TABED 1-24-157, date: 24.04.2024).*

Informed Consent: *Retrospective study.*

Footnotes

Author Contributions: *Surgical and Medical Practices: O.A., Ç.K., Y.Ö.U., T.T., Concept: Y.Ö.U., F.K., T.T., Design: F.K., T.T., Data Collection or Processing: O.A., Ç.K., E.G., G.T.G., Analysis or Interpretation: O.A., Ç.K., A.A.T., Literature Search: O.A., E.G., A.A.T., G.T.G., Writing: O.A., T.T.*

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An evaluation of the relationship between striae gravidarum and intra-abdominal adhesions in caesarean section

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Abstract

Objective: Recurrent cesarean deliveries are associated with intra-abdominal adhesions, and these adhesions affect maternal and neonatal morbidity. The aim of this study was to evaluate the relationship between the severity of striae gravidarum (SG) and intra-abdominal adhesions detected during cesarean section (CS).

Material and Methods: In this prospective, case-control study, women undergoing a second CS were divided into three groups according to the severity of SG (group 1 - no SG; group 2 - mild SG; group 3 - moderate to severe SG). Demographic and clinical characteristics, grade of intra-abdominal adhesions, Fitzpatrick skin type (FST), and serum 25-hydroxy vitamin D [25(OH)D] levels were assessed in all groups.

Results: A total of 150 cases were divided into three equal groups. There was no significant difference in body mass index among the groups ($p=0.155$). Although lower vitamin D levels were observed in group 3 compared to the other groups ($p=0.034$), the grade of adhesions was not associated with vitamin D level ($p=0.281$). All of the grade 2-4 adhesions occurred in mild to moderate cases of SG. Intra-abdominal adhesion was absent in 92% of CS ($p<0.001$) in pregnancies where SG was not detected. No intra-abdominal adhesions were observed in women with FST type 1 and in 80% of cases with type 6 skin, grade 2-4 adhesions were found ($p<0.001$).

Conclusion: Pregnant women with moderate SG and dark skin are at high-risk of increased incidence of intra-abdominal adhesions in subsequent CS. (J Turk Ger Gynecol Assoc. 2025; 26: 41-8)

Keywords: Adhesion, caesarean section, striae distensae, vitamin D

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Introduction

Striae gravidarum (SG), also known as striae distensae, is a dermatological condition that is particularly prevalent during pregnancy, affecting approximately 60-90% of women (1,2). The lesions develop predominantly on the skin of the abdominal wall, whereas the skin of the breasts, back, and proximal extremities are areas where this condition is less commonly observed (3). SG has been associated with several factors, including maternal obesity, gestational weight gain, family history, and genetic factors (4). SG may cause itching, discomfort, and psychological distress in pregnant women, as it is a permanent change in the appearance of the skin, and current treatments to prevent and treat SG have had limited success (1-4).

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Tensile strength and elasticity of the skin are related to structural changes in skin components, such as fibrillin, elastin, and collagen (5). The constant stretching of the extracellular matrix in the skin during pregnancy can lead to the remodeling of elastic fibers and the appearance of clinical striae in susceptible individuals (5). The Fitzpatrick skin type (FST) classification, originally developed to assess the susceptibility of the skin to burning during phototherapy, has also become a widely used system for categorizing skin color and ethnicity (6). However, the results of studies investigating the relationship between FST classification and SG formation have been inconsistent. One study found that light-skinned women had an increased risk compared to darker-skinned women (4), while another study found that darker-skinned women had an increased risk (7).

The balance between fibrin deposition and migration is of great importance in the process of normal peritoneal healing and adhesion formation (5,8). Complete degradation of fibrin leads to collagen production by fibroblasts, whereas ineffective collagen degradation leads to peritoneal adhesion formation (8). Adhesions are present in 95% of cases following abdominal surgery (8), and adhesions have been reported as a common complication of cesarean section (CS) (9). Intra-abdominal adhesions may cause abdominal discomfort, pain, and consequently reduced quality of life (10). In addition, adhesions could potentially complicate subsequent CSs, particularly in cases of emergency or multiple births (10,11). This is due to the increased difficulty of the surgical procedure, which can lead to complications, such as bladder damage and prolonged surgery time (10,11). In addition, intra-abdominal adhesions may also lead to an increased risk of birth asphyxia and maternal morbidity (11).

The objective of this study was to examine the association between the severity of abdominal SG, which occurs during pregnancy, and the grade of intra-abdominal adhesion formation following a history of CS deliveries.

Material and Methods

Written informed consent was obtained from all participants before the start of the prospective case-control study. Ethical approval was subsequently granted by the Etlik Zübeyde Hanım Women's Health Training and Research Hospital Local Ethics Committee (approval number: 2021/50, date: 07.05.2021). The study included pregnant Turkish women who underwent CS at 37-40 weeks gestation in a tertiary care center between 2020 and 2023. The women had a singleton pregnancy with estimated fetal weight of 2000-4000 g and body mass index (BMI) of 18-30 kg/m^2. To minimize the effect of multiple CS on the results, only pregnant women with a single previous CS were included. Multiple pregnancies, women with comorbidities (e.g. hypertension, diabetes mellitus, Cushing's disease, etc.), connective tissue disorders (e.g. Marfan syndrome, etc.), those using corticosteroids, and those with conditions that may cause adhesion formation (e.g. pelvic inflammatory disease, other previous abdominopelvic surgery, and a history of endometriosis) were excluded.

The data set included information on age, parity, height, weight, gestational weight gain, comorbidities, family history of SG, lotions used during pregnancy to prevent SG, and skin type. In addition, serum 25-hydroxy vitamin D [25(OH)D] levels (ng/mL) were obtained. The lotions used by participants were of a mixed oil composition, exhibiting comparable constituents. The FST scoring system (12) was used to assess the women's skin types. The severity of intra-abdominal adhesions and SG were assessed using the Nair scoring system (13) and the Davey scoring system (14), respectively.

The patients' skin types were scored according to the FST scoring system (12). According to the FST classification, the types are as follows;

FST type 1: Individuals with a very fair complexion, frequent sunburns, no tanning, light eyes (blue-green), and yellow or red hair.

FST type 2: Individuals with a fair complexion, burn easily, tan poorly and have light blue eyes.

FST type 3: Individuals with dark white skin, tan after the first burn.

FST type 4: Individuals with light auburn tan, burns easily, tans easily, brown-black hair color.

FST type 5: Individuals with auburn tan, rarely burn, and tans easily.

FST type 6: Individuals with dark auburn or black tan, never burns, usually dark tan.

The intra-abdominal adhesions of the women were scored intra-operatively using the Nair scoring system (13) and the abdominal adhesions were graded into five categories as follows.

Grade 0: No adhesion.

Grade 1: Single band between viscera or from a single point on the viscera to the abdominal wall.

Grade 2: Two bands between viscera or from viscera to abdominal wall.

Grade 3: Intra-visceral mass, defined as a collection of viscera or intestines not adhering to the abdominal wall with more than two bands or the entire length of the intestines.

Grade 4 is characterized by the direct adhesion of viscera to the abdominal wall, regardless of the number and size of the bands.

The women's abdominal striae were scored using the Davey abdominal striae scoring system before CS (14). The skin of the abdominal wall was divided into four quadrants by the midline and horizontal lines passing through the navel, and the striae

for each quadrant were scored as 0 points clear skin, 1-point moderate striae, and 2-points multiple striae. The total score ranged from 0 to 8. The severity of SG was divided into three categories: 0 points, no SG; 1-2 points, mild SG; and 3-8 points, moderate to severe SG. The cases included in the study were divided into three groups: group 1, women with no SG; group 2, women with mild SG; and group 3, women with moderate-severe SG. The primary outcomes were the comparison of the demographic and clinical characteristics of the cases, the grade of intra-abdominal adhesions and the serum 25(OH)D levels between the three groups. Secondary outcomes included the division of intra-abdominal adhesions into three groups according to grade, followed by comparison of demographic and clinical characteristics, FST types, SG severity, and serum 25(OH)D levels.

A power analysis was conducted using the G*Power 3.1 program to determine the requisite sample size based on data from Chang et al. (4). When the gross enrollment index was set at 1, the alpha level was set at 0.05, and the desired power was 95%, resulting in a minimum sample size of 78, with 26 pregnant women in each group. In consideration of the findings of the power analysis, a total of 150 patients, 50 patients in each group, were included in the study.

Statistical analysis

Data analysis was conducted using SPSS, version 21.0 (SPSS, Inc., Chicago, IL, USA) and was evaluated at a 95% confidence level. Variables exhibiting normality were analyzed with the independent ANOVA test. The Kruskal-Wallis test was employed for variables that did not distribute normally. In the event of a statistically significant difference in the ANOVA test, multiple comparisons were conducted using the LSD test. Conversely, in the case of a significant difference in the Kruskal-Wallis test, the Mann-Whitney U test with Bonferroni correction was employed. The relationship between categorical variables was analyzed using the chi-square test.

Results

A total of 150 women were included, divided into three equal groups based on severity of SG. The groups were: group 1 - 50 women with no SG; group 2 - 50 with mild SG; and group 3 - 50 with moderate-severe SG. The most prevalent skin type was type 5, observed in 29.3% (n=44) of the study population, while the least prevalent was type 6, observed in 3.3% (n=5) of the study population. The majority of participants exhibited grade 0 adhesions (71.3%). The distribution of the severity of SG, skin type, and the grade of intra-abdominal adhesion in the study population is presented in Figure 1.

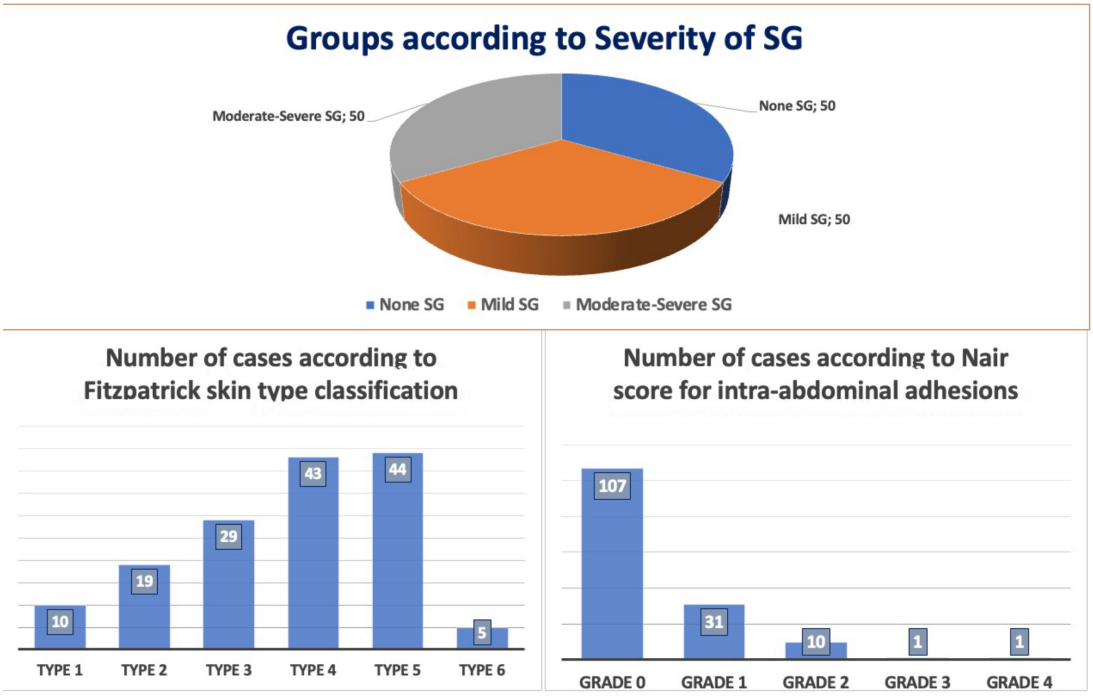

Figure 1. Distribution of study population according to severity of stria gravidarum, Fitzpatrick skin type, and grade of intra-abdominal adhesions in cesarean birth
SG: Striae gravidarum

Table 1 presents the demographic and clinical characteristics of the study groups. Group 3 was younger than group 1 (27.86±4.54 years vs. 30.24±5.83 years, p<0.05). There was no significant difference in the mean BMI of the groups (p>0.05). However, the serum 25(OH)D levels of the SG groups were significantly different. The mean 25(OH)D level was significantly lower in group 3 than in the other two groups (32.48±18.29 ng/mL in group 1, 31.82±20.73 ng/mL in group 2, and 24.12±13.10 ng/mL in group 3, p=0.034). There was no significant difference among the groups in terms of gravidity, parity, education status, profession, smoking, presence of comorbidities, and family history for SG (p>0.05). However, the use of oil lotion during pregnancy was significantly more common in group 2 compared to the other two groups (p=0.021).

The intrabdominal adhesion grade was significantly higher in group 3 compared to the other two groups (p<0.001). The proportion of subjects with grade 0 adhesion (none) was highest in group 1 (92%), whereas the proportions of subjects with grade 1 (34%), grade 2 (20%), grade 3 (2%), and grade 4 (2%) adhesions were higher in group 3 than in the other groups (p<0.05, Table 1).

A comparative analysis of the groups formed according to the grade of intra-abdominal adhesions is presented in Table 2. The demographic characteristics, age and BMI of the groups were found to be similar (p<0.05). In contrast with the findings presented in Table 1, no significant difference was observed between the grade of adhesions and 25(OH)D levels (p=0.281). The group with grade 0 adhesions, defined as the absence of any adhesions, exhibited markedly elevated rates of vaginal delivery when compared to the other groups (p=0.006). The absence of intra-abdominal adhesion was observed in 92% of CS performed on pregnancies where SG was undetected, a finding that was significant, as seen Table 2 (p<0.001). All of the grade 2-4 adhesions occurred in cases of mild to moderate SG. No intra-abdominal adhesion was observed in cases with FST type 1 skin (n=10) during CS. However, in 80% of cases with FST type 6 skin, grade 2-4 adhesions were found.

Table 1. A comparison of the severity of Striae Gravidarum across the groups

Variables		**Severity of striae gravidarum**			
		Group 1 No SG	**Group 2 Mild SG**	**Group 3 Moderate-severe SG**	**p**
		Mean ± SD or n (%)	**Mean ± SD or n (%)**	**Mean ± SD or n (%)**	
Age (y)		30.24±5.83	28.36±4.43	27.86±4.54	**0.044**[a]
Height (cm)		160.56±5.61	161.02±5.14	162.06±5.90	0.387[a]
Weight (kg)		80.16±12.06	83.46±8.40	85.92±11.89	**0.003**[b]
BMI (kg/m^2)		31.46±2.43	32.14±2.72	32.66±3.65	0.155[b]
Gestational weight gain (kg)		11.00±5.10	12.18±4.95	11.12±5.77	0.472[a]
25-hydroxy vitamin D level (ng/mL)		32.48±18.29	31.82±20.73	24.12±13.10	**0.034**[a]
Education status	Illiterate	1(2.0)	4 (8.0)	3 (6.0)	0.728[c]
	Primary school	9(18.0)	7 (14.0)	8 (16.0)	
	Middle school	17 (34.0)	13 (26.0)	13 (26.0)	
	High school	13 (26.0)	18 (36.09	20 (40.0)	
	Licence	10 (20.0)	8 (16.0)	6 (12.0)	
Profession	None	42 (84.0)	45 (90.0)	44 (88.0)	0.656[c]
	Yes	8 (16.0)	5 (10.0)	6 (12.0)	
Smoking	None	39 (78.0)	46 (92.0)	42 (84.0)	0.150[c]
	Yes	11 (22.0)	4 (8.0)	8 (16.0)	
Presence of comorbidity	None	48 (96.0)	46 (92.0)	46 (92.0)	0.651[c]
	Yes	2 (4.0)	4 (8.09	4 (8.0)	
Family history for SG	None	42 (84.0)	38 (76.0)	32 (64.0)	0.069[c]
	Yes	8 (16.0)	12 (24.0)	18 (36.0)	
Use of oil lotion during pregnancy	None	45 (90.0)	38 (76.0)	47 (94.0)	**0.021**[c]
	Yes	5 (10.0)	12 (24.0)	3 (6.0)	

Table 1. Continued

Variables		Severity of striae gravidarum			
		Group 1 No SG	Group 2 Mild SG	Group 3 Moderate-severe SG	p
		Mean ± SD or n (%)	Mean ± SD or n (%)	Mean ± SD or n (%)	
Gravidity	2	28 (56.0)	26 (52.0)	28 (56.0)	0.454[c]
	3	14 (28.0)	15 (30.0)	11 (22.0)	
	4	4 (8.0)	8 (16.0)	5 (10.0)	
	≥5	4 (8.0)	1 (2.0)	6 (12.0)	
Parity	1	37 (74.0)	36 (72.0)	34 (68.0)	0.488[c]
	2	9 (18.0)	11 (22.0)	8 (16.0)	
	3-4	4 (8.0)	3 (6.0)	8 (16.0)	
Number of children	1	37 (74.0)	37 (74.0)	34 (68.0)	0.691[c]
	2	9 (18.0)	9 (18.0)	8 (16.0)	
	3	4 (8.0)	4 (8.0)	8 (16.0)	
Number of abortus	0	37 (74.0)	38 (76.0)	41 (82.0)	0.571[c]
	1	10 (20.0)	11 (22.0)	6 (12.0)	
	2-3	3 (6.0)	1 (2.0)	3 (6.0)	
Number of vaginal birth	0	37 (74.0)	36 (72.0)	34 (68.0)	0.488[c]
	1	9 (18.0)	11 (22.0)	8 (16.0)	
	2-3	4 (8.0)	3 (6.0)	8 (16.0)	
Nair score	Grade 0	46 (92.0)	40 (80.0)	21 (42.0)	**<0.001[c]**
	Grade 1	4 (8.0)	10 (20.0)	17 (34.0)	
	Grade 2	0 (0.0)	0 (0.0)	10 (20.0)	
	Grade 3	0 (0.0)	0 (0.0)	1 (2.0)	
	Grade 4	0 (0.0)	0 (0.0)	1 (2.0)	

[a]: ANOVA test, [b]: Kruskal-Wallis test, [c]: Chi-square test. Bold is statistically significant. SD: Standard deviation, SG: Striae gravidarum, BMI: Body mass index. In the case of a significant difference in the ANOVA test, multiple comparisons were carried out with the LSD test, while in the case of a significant difference in the Kruskal-Wallis test, the Mann-Whitney U test with Bonferroni correction was used. Significant parameters with $p<0.05$ in post-hoc analysis; for age, group 1 > group 3; for weight, group 1 < group 2 and group 1 < group 3; for 25-hydroxy vitamin D level, group 1 > group 3 and group 2 > group 3.

Table 2. A comparative analysis of the groups according to the grade of intra-abdominal adhesions

Variables		Grade of intra-abdominal adhesions according to Nair score			p
		Grade 0	Grade 1	Grade 2-4	
		Mean ± SD or n (%)	Mean ± SD or n (%)	Mean ± SD or n (%)	
Age (y)		28.92±5.04	27.55±5.05	31.25±4.43	0.091[a]
BMI (kg/m^2)		32.07±3.07	32.06±3.07	32.25±2.34	0.650[b]
Height (cm)		161.18±5.31	160.97±5.89	162.17±7.15	0.813[a]
Weight (kg)		83.22±11.63	82.19±9.92	85.33±9.41	0.576[b]
Gestational weight gain (kg)		11.35±5.07	10.84±5.98	13.75±4.96	0.256[a]
25-hydroxy vitamin D level (ng/mL)		28.64±15.96	33.81±23.90	25.75±16.67	0.281[a]
Education status	Illiterate	5 (62.5)	2 (25.0)	1 (12.5)	0.707[c]
	Primary school	16 (66.7)	6 (25.09	2 (8.3)	
	Middle school	30 (69.8)	11 (25.6)	2 (4.7)	
	High school	37 (72.5)	10 (19.6)	4 (7.89)	
	University	19 (79.2)	2 (8.3)	3 (12.5)	

Table 2. Continued

Variables		Grade of intra-abdominal adhesions according to Nair score			p
		Grade 0	Grade 1	Grade 2-4	
		Mean ± SD or n (%)	Mean ± SD or n (%)	Mean ± SD or n (%)	
Smoking	None	90 (70.9)	27 (21.3)	10 (7.9)	0.934[c]
	Yes	17 (73.9)	4 (17.4)	2 (8.7)	
Family history for SG	No	79 (70.9)	23 (20.59)	10 (8.9)	0.904[c]
	Yes	28 (73.79)	8 (21.1)	2 (5.3)	
Use of oil lotion during pregnancy	No	89 (68.59)	29 (22.3)	12 (9.2)	0.190[c]
	Yes	18 (90.09)	2 (10.0)	0 (0.0)	
Gravidity	2	57 (69.5)	20 (24.4)	5 (6.1)	0.367[c]
	3	32 (80.0)	6 (15.0)	2 (5.0)	
	4	11 (64.79)	3 (17.6)	3 (17.6)	
	≥5	7 (63.6)	2 (18.2)	2 (18.2)	
Number of children	1	77 (71.3)	26 (24.1)	5 (4.6)	**0.015[c]**
	2	20 (76.9)	4 (15.4)	2 (7.7)	
	3	10 (62.5)	1 (6.3)	5 (31.3)	
Number of vaginal birth	0	75 (70.1)	27 (25.2)	5 (4.7)	**0.006[c]**
	1	23 (82.1)	3 (10.7)	2 (7.1)	
	2-3	9 (60.0)	1 (6.7)	5 (33.3)	
Severity of SG	None SG	46 (92.0)	4 (8.0)	0 (0.0)	**<0.001[c]**
	Mild SG	40 (80.0)	10 (20.0)	0 (0.0)	
	Moderate-severe SG	21 (42.0)	17 (34.0)	12 (24.0)	
FST score	Type 1	10 (100.0)	0 (0.0)	0 (0.0)	**<0.001[c]**
	Type 2	17 (89.5)	2 (10.5)	0 (0.0)	
	Type 3	24 (82.8)	3 (10.3)	2 (6.9)	
	Type 4	30 (69.8)	11 (25.6)	2 (4.7)	
	Type 5	25 (56.8)	15 (34.1)	4 (9.1)	
	Type 6	1 (20.0)	0 (0.0)	4 (80.0)	

[a]: ANOVA test, [b]: Kruskal-Wallis test, [c]: Chi-square test. Bold is statistically significant. FST: Fitzpatrick skin type, SD: Standard deviation, SG: Striae gravidarum, BMI: Body mass index

Discussion

The capacity to anticipate the occurrence of intra-abdominal adhesions in subsequent CSs is important for obstetricians. The findings of this study indicate that as the severity of SG increases and the skin color darkens, the degree of intra-abdominal adhesions also increases. Furthermore, an increased rate of adhesion may be encountered in CS of pregnancies in this group of women.

Chang et al. (4) reported that family history, race, and genetic factors are more indicative of SG development than pre-pregnancy BMI, mean gestational weight gain, mean percent weight gain, and mean change in BMI during pregnancy. The present study, conducted with Turkish women with similar family history rates, revealed that the moderate-severe SG group exhibited higher weight, despite being younger than the other groups. As in our study, Davey, who devised the SG classification, demonstrated that women with higher BMIs were more likely to develop SG (15).

A paucity of published studies has investigated the relationship between the severity of SG during pregnancy and serum 25(OH) D levels. In a study by Hocaoglu et al. (16), serum 25(OH)D levels were measured in 91 primigravid female patients. The results indicated that women with normal serum 25(OH)D levels (≥30 ng/mL) had a lower risk of having SG than women with low serum 25(OH)D levels. Similarly, in the present study, 25(OH)D levels were found to be significantly lower in the moderate-severe SG group (24.12±13.10 ng/L) compared

to the non-SG and mild SG groups. Unfortunately, vitamin D deficiency is currently considered to have become a global epidemic and during pregnancy, vitamin D supplementation is recommended (17). Nevertheless, no significant association was found between intra-abdominal adhesions and vitamin D in our study. To our knowledge, this is the first study to investigate the relationship between intra-abdominal adhesions and vitamin D, and further randomized controlled trials are needed to provide clearer information.

A review of topical methods used to prevent SG (18), especially in pregnancy, found that there was limited evidence that massages with almond oil can prevent and/or reduce the severity of SG. Furthermore, cocoa butter and olive oil were not effective in preventing SG or reducing the severity of lesions. In the present study, the mild SG group used more lotions containing mixed oils with more ingredients than the moderate-severe group. Further research is required to elucidate the pathogenesis of SG, as reliable methods of prevention are scarce. Furthermore, the heterogeneity of topical methods and the lack of strong evidence from well-designed, randomized controlled trials necessitate further investigation.

The grades of intra-abdominal adhesions demonstrated a significant increase in accordance with the Nair score in women who exhibited heightened SG severity, as classified by the Davey score, prior to their second CS. In a case-control study by Elprince et al. (19), involving 408 women, thick intraperitoneal adhesions were observed in 43.75% of women with severe SG. Additionally, Davey scores and Vancouver scores, which are used to classify cesarean scars, demonstrated highly significant predictive performance for intraperitoneal adhesions. In a similar study by Abbas et al. (20), 300 women were observed. The results indicated that dense adhesions were significantly higher (57.4%) in the severe SG group. A significant positive moderate correlation was observed between the Nair score and the Davey score ($r=0.541$). The authors concluded that the only variable associated with an increased risk of pelvic adhesions was the Davey score >2. Furthermore, another study reported higher rates of intraperitoneal adhesions in women with no or mild striae than in those with severe striae (67.3%, 65.9%, and 36.3%, respectively) (21).

Consequently, abdominal striae and CS scar were identified as significant predictors of intraperitoneal adhesions, as evidenced by the findings of earlier studies and the present one (19-21). Nevertheless, Jaafar et al. (22) observed in a comparable study involving 100 patients that abdominal scar width, collapsed scar, and striae color grading were significantly associated with intra-abdominal adhesions. However, they noted that these markers may not be reliable due to their low validity. One of the few studies on this subject, by Altınboğa et al. (23) in 115 patients, showed a significant increase in adhesion density with increasing skin color. Furthermore, the frequency of abdominal adhesions increased significantly with increasing Fitzpatrick score (23).

It is of the utmost importance to take all possible measures to minimize the incidence of pelvic adhesions in cases of repeat cesarean deliveries. Two principal strategies are currently being investigated: peritoneal closure and/or the use of adhesion barriers during cesarean deliveries (24). A significant number of researchers are engaged in the pursuit of efficacious methodologies for the prevention of adhesions (24,25). Individual studies employing barrier materials, Ringer's lactate solution and anti-adhesive components have yielded encouraging outcomes in the prevention of postoperative adhesions (24,25). A 2020 Cochrane review, which addressed the efficacy of barrier agents in the prevention of adhesions following gynecological surgery (25), concluded that certain absorbable adhesion barriers reduce the incidence of adhesion formation after laparotomy. However, no conclusions specifically pertinent to cesarean deliveries were made since no published randomized controlled trials were available. At present, there is no standardized agent in use at our clinic. However, peritoneal closure is a routine procedure in cases where adhesion is present in cesarean birth. It seems reasonable to suggest that the most effective strategy for the prevention of post-cesarean adhesions is to reduce the incidence of primary CS and to provide appropriate support to families and obstetricians.

Study Limitations

This study is, to the best of our knowledge, one of the first to show an association between FST and intra-abdominal adhesions. The formation of intra-abdominal adhesions increased significantly with increasing FST category. A more accurate evaluation of the relationship between SG and intra-abdominal adhesions may be achieved by including only women who will have a second CS and excluding conditions that may act as cofactors for adhesion formation, such as a history of multiple CS, previous intra-abdominal surgery, pelvic inflammatory disease and endometriosis. In addition, FST were assessed for all groups and the potential influence of skin color on adhesion formation was also considered. As a limitation, severe and moderate SG were evaluated together as there were only seven cases in the severe group.

Conclusion

The results of this study suggest that as the severity of SG and the FST score increases, the incidence of intra-abdominal adhesions at second Cesarean delivery also increases significantly. It is therefore important for obstetricians to be aware that pregnant women with severe SG and dark skin are

at higher risk of adhesion formation after cesarean delivery and to counsel them appropriately regarding the potential adverse maternal and perinatal outcomes that may occur with subsequent CSs.

Ethics

Ethics Committee Approval: *Ethical approval was subsequently granted by the Etlik Zübeyde Hanım Women's Health Training and Research Hospital Local Ethics Committee (approval number: 2021/50, date: 07.05.2021).*

Informed Consent: *Written informed consent was obtained from all participants before the start of the prospective case-control study.*

Footnotes

Author Contributions: *Surgical and Medical Practices: Y.A.R., F.B.F., S.Y.E., B.S.Ü., Concept: Y.A.R., A.A., R.S.K., Y.E.Ü., Design: Y.A.R., A.A., R.S.K., Y.E.Ü., Data Collection or Processing: Y.A.R., N.M., Analysis or Interpretation: Y.A.R., A.A., T.K., Literature Search: Y.A.R., A.A., T.K., Writing: Y.A.R., A.A., F.B.F., S.Y.E., N.M., B.S.Ü., T.K., R.S.K., Y.E.Ü.*

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Ovarian cancer and isolated cardiophrenic lymph nodes metastases: a systematic review

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Abstract

Currently, there is limited information available on the best course of action for advanced epithelial ovarian cancer (OC) with isolated extra-peritoneal disease in the cardiophrenic lymph nodes. Recently, there have been numerous reports of successful surgical removal of metastatic cardiophrenic lymph nodes in patients with OC, mostly during primary or interval cytoreduction procedures. However, the optimal management of isolated, extra-peritoneal cardiophrenic lymph node metastasis (ICLNM) remains unclear, since this clinical scenario is rather uncommon in OC and chemotherapy is so far the indicated treatment for patients with from advanced stage disease. We searched the English-language literature for cases of OC with ICLNM or recurrence, evaluating the feasibility and safety of surgical excision. From 2009 to 2022 only 11 cases were reported. In seven the tumor was of serous histology. ICLN was detected in five cases with primary disease and in the remaining six it was recurrence of OC. The primary disease was treated in 10/11 patients with primary cytoreduction while the other received systemic chemotherapy. The ICLNM was removed in all the patients, in 10 via video-assisted thoracic surgery and in one via transdiaphragmatic incision. Median follow-up was 10 months. (J Turk Ger Gynecol Assoc. 2025; 26: 49-54)

Keywords: Ovarian cancer, cardiophrenic lymph nodes, isolated metastasis

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Introduction

The existing literature reports that cardiophrenic lymph node metastasis (CLNM) affects 2.3% of ovarian cancer (OC) patients. Extra-abdominal metastases associated with OC were once considered a very poor prognostic indicator, with systemic therapy being the only treatment modality. Recently, extra-abdominal cytoreductive surgery has become increasingly popular as a proactive treatment choice for certain patients with thoracic metastases. This approach has been shown to enhance outcomes and extend survival for such patients, highlighting the importance of early intervention in these cases. Interestingly, the outcome for patients with CLNMs arising from OC is estimated to be less poor than that of other International Federation of Gynecology and Obstetrics (FIGO) stage IVB OC patients, reaching 68.9-72.3 months (1). Unfortunately, despite the better prognosis and the rising incidence of these cases, a consensus guideline approach has not yet been validated, and although much has been written regarding the management of intra-abdominal lymph node metastatic sites, little is known about the optimal approach in cases of isolated cardiophrenic lymph node metastasis (ICLNMs). More specifically, a recent study by Boria and Chiva (2) proposed that cardiophrenic lymph node resection can be safely performed in selected patients, but no survival benefit has been demonstrated to date. However, a recent study by Nasioudis et al. (3) indicated a higher survival rate in patients with OC isolated distant lymph node metastases compared to those with stage IV disease from other metastatic sites, potentially even comparable to patients

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with stage IIIC disease. As a result, the removal of isolated cardiophrenic lymph nodes in FIGO stage IVB OC continues to be a topic of debate, and the present analysis seeks to clarify the feasibility and outcomes of such cytoreductive surgery in this specific group. Consequently, the reported cases of solitary extra-peritoneal cardiophrenic metastasis of OC that underwent surgical intrathoracic debulking were reviewed.

Material and methods

Data sources

The electronic databases PubMed and Google Scholar were searched by two authors (V.P. and A.F.). The literature search was performed in accordance with the preferred reporting items for systematic reviews and meta-analyses guidelines (4). The search strategy used in both databases, included the combination of the keywords: (OC OR tubal OR peritoneal) AND (isolated cardiophrenic lymph node) AND (metastasis OR involvement). All databases were searched up to December 2023. The references of relevant articles were also manually searched for additional studies. Studies in languages other than English were excluded. The initially identified studies were screened, based on their title and abstracts against inclusion criteria. At the end of this initial search, all records considered eligible were included for full-text assessment.

Study selection criteria

All selected articles were in English and referred to studies on humans. Moreover, for a study to be included and it had to demonstrate histological or radiological diagnosis of ICLNM of an ovarian, tubal or peritoneal carcinoma. Review articles and studies with patients diagnosed with multiple metastatic sites and/or extended disease were excluded. Figure 1 demonstrates the selection strategies. All authors' agreed by consensus regarding the final decision on both inclusion and exclusion of the papers.

Results

The initial search yielded 27 citations, with an additional three studies included from manual bibliography searches. Four studies were excluded for being literature reviews, nine for focusing on radiological criteria, and 12 for discussing management options or surgical techniques related to cardiophrenic lymph node resection. Ultimately, five articles were chosen for analysis, as summarized in Table 1 (5-9).

Study results

Five studies with a total of 11 patients were investigated. In seven (63.6%) the primary tumor was of serous histology. By the time of the diagnosis of ICLNM, four (36.4%) had a primary and six (54.5%) had recurrent disease. For the treatment of the primary disease, nine (81.9%) underwent primary

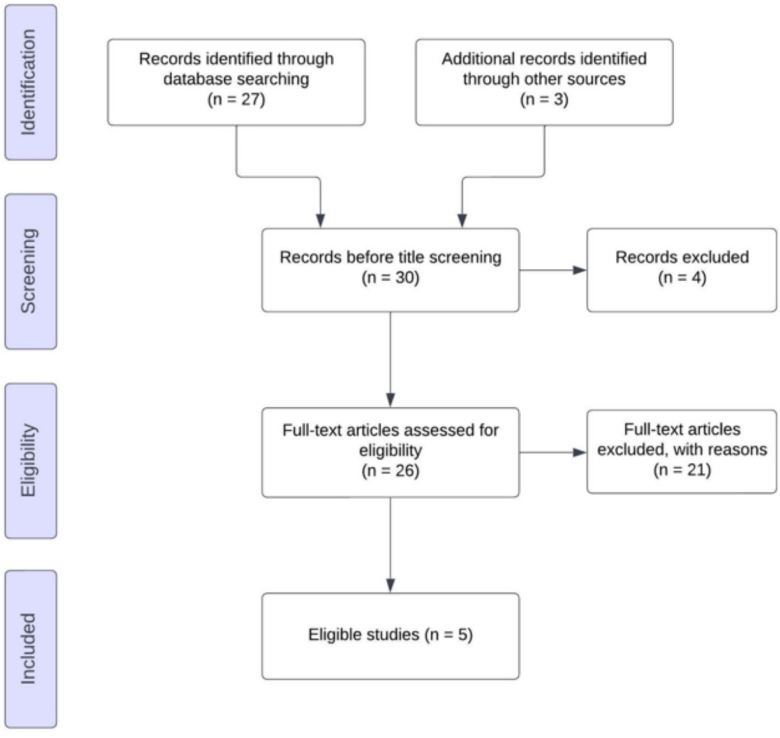

Figure 1. PRISMA flow-diagram

Table 1. Studies reporting data on isolated cardiophrenic lymph node metastasis in patients with ovarian cancer.

First author year	Number of patients	Age of patient (range)	Serous histology	Other histology	Primary disease	Recurrence	Main symptoms	Primary disease treatment		ISLN resection	LN treated with systematic therapy	Follow-up (mo)
								Chemo therapy	Surgical debulking			
Case series												
Euscher, (2004)	8	Median: 49.5 (30-68)	8	0	7	0	1: Neurological paraneoplastic syndrome	7	4	4	2	Median: 29 (12-166)
Blanchard, (2007)	7	NM	NM	NM	0	7	NM	NM	7	5	2	NM
Case reports												
Piura, (1989)	1	48	1	0	1	0	Mass	1	1 (secondary)	1	1	20
Mayadevi, (2005)	1	59	1	0	1	0	Mass	0	1	0	1	24
Gontier, (2006)	1	76	1	0	0	0	Mass	0	1	0	1	24
Keepanasseril, (2008)	1	33	0	1	1	0	Mass	0	1	0	1	10
He, (2013)	1	60	1	0	1	0	Bilateral mass	0	1	0	1	6
Puri, (2015)	1	65	0	1	0	1	Mass	0	1	0	1	NM
Kemal, (2016)	1	64	1	0	1	0	Mass	1	0	0	1	NM
Dhilon, (2013)	1	68	0	1	0	1	No	0	1	0	1	NM
Holmess, (2017)	1	32	0	1	0	1	Mass	0	1	1	0	NM
Tanaka, (2018)	1	65	1	0	0	1	Immobile mass	0	1	1	1	20
Baharudin, (2019)	1	28	1	0	1	0	Mass	1	1	1	0	12
Piciu, (2020)	1	75	0	1	0	1	Mass	NM	NM	0	1	NM

NM: Not mentioned

cytoreduction while one (9%) received a combination of neoadjuvant chemotherapy (NACT) and surgical resection. The median age at the time of diagnosis of the metastases was 50 years. The ICLNM was found at the right side in two patients (18%), on the left side in one (9%) and bilaterally in another two patients (18%) while for the other five the side was not specified. All 11 patients (100%) underwent surgical excision of the ICLN, in one case in conjunction with systemic therapy, but the included studies (5-9), showed variations in the method of treatment. Video-assisted thoracic surgery (VATS) was the most popular approach (n=10, 90.9%) while only one patient (9%) underwent transdiaphragmatic incision. Complications were reported in two (18%), one with pleural effusion that required medical treatment after VATS and one with postoperative chylothorax and chest liver herniation following a transdiaphragmatic resection. The mean follow-up of the patients was 10 months.

Discussion

The CPLNs are located in the thoracic cavity, typically positioned behind the sternum and between the diaphragm and the heart. These lymph nodes receive drainage from various organs, including the diaphragm, anterior part of the liver, pleura, and anterior chest wall. Diagnosing and reducing intrathoracic metastases originating from OC present significant challenges. Limited information is available on intrathoracic metastases specific to OC. Nevertheless, advances in surgical techniques, instrumentation, and perioperative care have made intrathoracic diagnosis and reduction safe and effective procedures (5).

This review showed that surgical lymph node dissection may be a viable management strategy for certain subsets of OC patients with ICLNM, with the goal of achieving improved survival rates. Our results align with a recent study from the Memorial Sloan Kettering Cancer Center team, which highlighted the safety and feasibility of intrathoracic cytoreduction in 178 advanced-stage OC patients. The study also suggested that this approach could result in significantly enhanced progression-free survival (PFS) and overall survival (OS) in carefully selected patients who can undergo tumor-free surgery, despite having extra-abdominal tumor burden. Furthermore, in the same study it was stated that instead of automatically considering NACT for patients with operable stage IV disease, it is now recommended to assess their eligibility for primary debulking surgery (PDS). Recent data shows promising results when comparing NACT to PDS, suggesting that high tumor burden stage IV patients may not always require NACT, as previously suggested (10).

The original classification of FIGO stage IV OC grouped patients based on disease burden, prognosis, and management recommendations. This included extra-peritoneal disease, such as pleural effusion, parenchymal liver metastases, and extra-abdominal lymph node involvement, such as the supraclavicular lymph nodes. However, in the 2014 revision, patients with pleural effusion were considered a separate category from those with parenchymal disease or metastases to extra-abdominal lymph nodes. Nasioudis et al. (3) reported that isolated distant lymph node metastases have a more favorable prognosis than stage IV disease with metastases in other sites, and are comparable to patients with stage IIIC disease. Zang et al. (11) compared stage IV OC patients with extra abdominal or intrahepatic metastasis and found that women with isolated supraclavicular lymphadenopathy or malignant pleural effusion had better survival rates than other stage IV patients. A study by Deng et al. (12) with 1,481 patients showed that the site of distant metastases significantly affects the overall prognosis in FIGO stage IV OC. These authors estimated a lower OS for parenchymal metastases compared to distant lymph node metastases. Similarly, in a comprehensive study, Hjerpe et al. (13) found that women with stage IV serous OC who only have lymph nodes as distant metastatic sites tend to have a longer survival compared to other stage IV patients. A recent review by Pergialiotis et al. (14) demonstrated that in OC patients with isolated lymph node recurrence (ILRN), survival was prolonged compared to recurrences in other sites. This type of recurrence seems to be less aggressive and can be treated with a combination of secondary cytoreduction and standard chemotherapy in selected cases (14), aligning with the previous research conducted by Uzan et al. (15), which proposed that patients with a prior isolated OC nodal recurrence may have a more favorable prognosis when undergoing surgical resection followed by chemoradiation or radiation therapy.

Regarding the identification of such rare metastases, radiology appears to play an essential role. More specifically, 10 out of 11 patients diagnosed with ICLNM were operated with VATS, meaning no abdominal surgery was performed. As a result, in those cases the isolated cardiophrenic metastasis diagnosis was based on imaging, in seven cases by computed tomography (CT) and in the other three by fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning. Only one patient underwent abdominal exploration during the complete cytoreduction and the initial radiological finding was confirmed by anatomopathological analysis. Typically, CT is the preferable radiological method for OC patients surveillance and staging and usually cardiophrenic lymph nodes larger than 5 mm are considered suspicious. However, according to Boria and Chiva (2), the confirmation rates in the final histological examination vary from 45-95%. Nevertheless, Hynninen et al. (16) demonstrated the inferiority of FDG PET/CT in detecting histologically confirmed supradiaphragmatic lymph node metastases when compared to conventional CT

and highlighted the correlation of this finding to the presence of ascites and subdiaphragmatic carcinomatosis compared to patients without it. Another possible method to localize suspicious CPLNs and to guide their surgical eradication was presented by Moro et al. (17) who performed intraoperative transdiaphragmatic ultrasound during a cytoreduction surgery and after the abdominal debulking was completed.

The optimal approach for dissection remains uncertain. In the majority of the centers that have reported cases of resection of cardiophrenic LNs, VATS has been used, but also transdiaphragmatic incision has been successfully conducted by Leray et al. (8). Interestingly, Minig et al. (18) and Yang et al. (19) proposed the subxiphoid approach to resect cardiophrenic lymph nodes, suggesting that it reduces the possibility of opening the pleural cavity, since it avoids a diaphragmatic incision and in most of the cases liver mobilization. Khatib et al. (20) also presented their approach via the subxiphoid route in order to resect prepericardiac and costophrenic lymph nodes without opening the diaphragm and with acceptable morbidity for patients.

Nevertheless, none of the studies manages to quantify any survival benefit of thoracic cytoreduction since the impact of ICLNM dissection has not been fully elucidated. Moreover, complications such as pleural effusion and pneumothorax are relatively common, while major complications also occur in 0-9% of patients (2). In our analysis, two cases (20%) reported complications: one involved pleural effusion requiring medical treatment after a VATS approach, and the other included chylothorax, atelectasis, and thoracotomy for chest liver herniation following a transdiaphragmatic incision.

However, a recent meta-analysis (21) has demonstrated that optimal tertiary cytoreduction surgery with an absence of residual tumor was associated with improved OS and PFS compared to suboptimal tertiary cytoreductive surgery and this is in line with previous retrospective analysis of tertiary cytoreduction (22,23). Recently Bruno et al. (24) reported proposed minimally invasive tertiary cytoreductive surgery because a patient presented with a pelvic ILRN, with a highly predictable optimal cytoreduction. Their experience confirmed that tertiary cytoreductive surgery may be considered an effective therapeutic option for management of ILRN, even in patients with *BRCA 1* or *BRCA 2* mutation-associated carcinoma already treated with PARPi. In particular, the personalization of the strategy and the achievement of a complete cytoreduction must be the aim of the treatment of these kind or recurrences. In this context, surgical excision may play a role if curative treatment for the abdominal disease is feasible. CLNMs are rare, with fewer than 10 eligible patients identified for this review. The scarcity of reported cases may be attributed to variations in the quality of radiological diagnosis of metastatic nodes. Most primary data comes from case series and reports, posing risks of selection and publication biases and only two databases (PubMed and Google) were included, thus representing a slight selection bias. The limitations in primary data restrict definitive conclusions on the optimal treatment of ICLNM. Therefore, the conclusions drawn are not recommendations due to the small sample sizes.

Conclusion

Our findings may be less robust than original, higher-quality evidence. Further single-center case series are unlikely to significantly contribute to the existing knowledge base. Therefore, there is a need for more extensive and impactful research in this area. Due to the rarity of ICLNM, traditional study recruitment methods may not reach the necessary patient numbers for meaningful results, making a multinational registry essential for additional data. Furthermore, expert consensus opinions would benefit clinical teams treating patients with ICLNM. Currently, this review serves as a summary of the current understanding in this field, offering a contemporary overview to assist clinicians in treating patients with ICLNM from primary or recurrent OC.

Footnotes

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

Oral health protection and restorative approaches in the puerperal period

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Abstract

There is a growing need for dental treatments in women during the puerperal period as a consequence of hormonal and physiological changes that occur. There are effective methods that dentists can apply while treating patients in the puerperal period and while ensuring the maintenance of treatment. The framework of these methods covers a wide range of subjects, from the examination and diagnosis process of the dentist to the treatment protocols and the oral hygiene motivation of the patient. This review focuses on restorative treatment protocols that dentists would apply to patients in the puerperal period and the maintenance of these treatments. (J Turk Ger Gynecol Assoc. 2025; 26: 55-61)

Keywords: Breastfeeding, dental treatment, oral health, puerperium

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Introduction

The period that begins with the separation of the placenta and continues until the vanishing of physiological changes in the mother's body that occurred during pregnancy and the returning of the genital organs to their pre-pregnancy state is called the puerperium, and the mother in this period is called the "puerpera". The puerperium covers roughly 6-8 weeks after birth. This period is also important for oral health because of the many hormonal changes that may occur in pregnancy.

Postpartum women may encounter some problems with dental health and care due to hormonal changes during or after pregnancy or due to different circumstances, brought about by the new situation. In addition, most of the dental treatments needed during pregnancy are usually postponed until after birth. During pregnancy, practices, such as treatments of gestational gingivitis, which are anticipated not to lead to any problems, non-radical tooth extractions, and restorative treatments are frequently performed, but long-term treatments and radical treatments are generally avoided. Therefore, the postpartum period constitutes a time in which postponed procedures during pregnancy may be performed. Thus, determining the proper treatment strategies is important to provide the patient comfort and for the success of the treatment (1-5).

Gingivitis or bleeding tender gums is the most common dental problem and affects about 60-75% of pregnant women (2). During pregnancy, there is an increase in the gingival tissue inflammatory response to dental plaque biofilm due to the elevated levels of steroid hormones. Although it is believed that pregnancy-induced hormonal changes decline postpartum, periodontal tissues often do not revert to their pre-pregnancy state immediately, and oral inflammation may last up to three months postpartum (4,6).

Ensuring the oral health of women during the puerperal period is essential as it will also affect their general health status. However, mothers with poor oral hygiene and a high rate of

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cariogenic bacteria (especially, *Streptococcus mutans*) in the oral cavity may infect their newborn babies with cariogenic bacteria beginning from birth. The risk of caries formation increases in the period after tooth eruption in children who are infected with cariogenic bacteria during the early period. Studies have reported that bacteria that cause caries in children and bacteria samples from the mouths of mothers are approximately 70% similar (7).

There are many obstacles to the treatment of dental problems and ensuring oral care for women after childbirth. These obstacles range from spending less time on oral hygiene while caring for the baby to the anxiety that the diagnosis and treatment procedures to be applied may affect the baby (8,9). However, similar to the pregnancy period, it is possible to provide dental treatment and oral hygiene safely in the postpartum period (4).

Examination and treatment approaches in postpartum patients

The dentist who examines the puerperal patient must embrace the following three major principles:

1. Dental caries does not only impact oral health. Oral health is an integral part of general health status;
2. In the puerperal period, the mother's health status is directly associated with the health of her breastfed baby;
3. A multidisciplinary team approach (dentist, obstetrician, pediatrician) is the safest and most effective way to provide the patient with appropriate dental treatment. Achieving good communication between the team members treating the patient(s) is vital to developing an appropriate treatment plan and ensuring coordination during the treatment process.

First of all, it should be kept in mind at the stage of informing the patient that the puerpera feels unease about whether the chemicals to be used in the treatments will pass from breast milk to the baby, whether the breast milk will be affected by the radiographic methods used, and whether the drugs to be used during the treatment may affect the baby. Another factor that should be considered is that the time of the mother who comes to the clinic after entrusting her baby to a caregiver is limited. Therefore, these patients may request that their treatments are administered within a limited duration, and their appointments are arranged according to the nursing and sleeping times of the baby.

In the puerperal period, if the patient does not have time for treatment in the clinic or if regular visits to the clinic would pose an issue, other care and treatment methods that can be applied at home may be recommended. Some of these recommendations are also valid for patients who cannot sit on the dental chair for a long time due to their health conditions. If the patient cannot move with ease or sit comfortably due to extensive episiotomy or various degrees of vaginal or perineum lacerations but also needs urgent dental treatment, it may be necessary to provide ergonomic solutions, such as an orthopedic sitting ring. Besides, there is a tendency to postpone dental treatments to the time after the breastfeeding period in this patient group (8-12). The factors affecting the tendency of postponing dental treatment to the time after the breastfeeding period in puerpera are given in Table 1.

Treatment modalities

When planning treatment modalities, it will be more appropriate to apply the rules of minimally invasive dentistry, especially in the first session, concerning the patient's limited time. The prevention of tooth decay in the puerperal period is important because it is difficult for puerpera to attend recurring clinical appointments (13). Coronal and root caries, gingival and periodontal diseases, or soft tissue lesions can be seen in women who have had frequent vomiting during pregnancy and neglected oral hygiene due to extreme nausea. The methods used in the prevention and control of caries are shown in Table 2 (14-17).

Table 1. Factors affecting the tendency of postponing dental treatment to the time after breastfeeding period in puerpera

• Absence of a person to take care of the baby during the treatment procedure.
• The anxiety of the mother concerning the harmful effects of the X-ray beam to be exposed for diagnosis processes may be passed on to the baby through breastfeeding.
• The mother getting tired more quickly due to hormonal changes in the puerperal period.
• The mother getting tired more quickly during this period due to irregular sleep and intense activity.
• The mother's anxiety that she may carry harmful microorganisms from the outer environment to her baby.
• The anxiety of the mother that the anesthetic agents to be administered may pass to the baby through breastfeeding.
• The anxiety of the mother that the chemicals used during treatment could be passed to the baby through breastfeeding.
• The mother's anxiety that the drugs administered before and after the treatment can be passed to the baby through breastfeeding.
• Postpartum depression.

Table 2. The methods used in the prevention and control of caries

The methods used in the prevention and control of the caries
• Elimination of cariogenic factors with dietary control and good oral hygiene.
• Elimination of cariogenic microorganisms using anti-cariogenic agents.
• Topical application of proper agents to reclassify the partially decalcified dentin matrix and provide resistance to later decalcifications.
• Removal of dentine showing signs of active cariosity.
• Protection of intact dentine, which is at risk with restorative procedures.

Covering the fissures that are prone to the formation of caries on the posterior teeth by the dentist with hard and waterproof plastic material (fissure sealant) prevents the emergence of caries. Furthermore, da Costa et al. (18) reported that there was a significant increase in the amount of mercury in breast milk when a large number of amalgam fillings are applied during the restorative treatment.

Opening minimal cavities with a laser may be preferred, as it will shorten the duration of the process. In addition, this method can be used to provide resistance to caries formation. Of note, epulis gravidarum can be removed by laser without bleeding if it has not regressed spontaneously after birth. During pregnancy, dentine sensitivity may occur due to mineral loss in the neck of the teeth due to increased gastroesophageal reflux and improper brushing. This sensitivity can be alleviated using laser applications (19).

In addition, many interventions that are postponed during pregnancy, such as complicated tooth extractions, tooth whitening procedures, and crown-bridge prostheses, may be performed safely during the puerperal period. Since the substances formed during the decomposition of carbamide peroxide, used in tooth whitening, are naturally contained in breast milk, there is no need to take special precautions or stop breastfeeding during their use (20).

There may be patients who cannot be mobilized due to various complications in the early puerperal period. In such cases, mobile dental units can be used for on-site diagnosis and treatment or atraumatic restorative treatment can be given.

Radiological examinations during pregnancy and puerperal periods.

Radiological examinations routinely used in dentistry practice do not lead to problems for puerpera. Thus, there should be no hesitation in using these imaging modalities to make a rapid and accurate diagnosis. While X-rays are taken, a radiation-protective apron should be provided to the puerpera, as for any patient.

In rare cases, if radiopharmaceuticals must be used, breastfeeding should be stopped for the half-life of the radiolabeled compounds. In such a case, the mother should feed the baby before the procedure, express and store her breast milk, make the subsequent feedings with stored milk, and keep the baby away from her own body (21,22).

Drug use in dental treatment during the puerperal period

It is possible that mothers may avoid dental treatment because of concerns that the drugs used during the breastfeeding period may pass into the milk and lead to adverse effects for her baby. Since most drugs are excreted into breast milk, the main problem here is whether the amount of the drug passed into breast milk is likely to cause a clinically significant adverse effect on the baby. Drugs with a relative infant dose below 10%, short half-life, high plasma protein binding and low-fat solubility are generally deemed to be usable in breastfeeding women. However, more detailed reviews for each drug to be used during the breastfeeding period can be found on the LactMed search engine (www.nlm.nih.gov Drugs and Lactation Database) (20). Usage information about frequently used drugs in the puerperal period is given in Table 3.

Since the gaps between the mammary gland alveolar cells are larger in the first two weeks after delivery, many drugs can pass into breast milk more easily during this period (23). Also, infants, especially those born prematurely or with low birth weight, are more susceptible to drug effects within the first two months, and therefore should be closely monitored for possible adverse effects.

Antibiotics

Maternal antibiotic use carries risks for the infant, such as allergic reactions, disruption of the intestinal flora, diarrhea, and candidiasis. For example, the use of maternal ampicillin frequently leads to diarrhea and candidiasis in the infant. Also, moxalactam, a third-generation cephalosporin, may cause gram-positive colonization and enterocolitis in the infant gastrointestinal system. In addition, metronidazole may often cause loose stools, feeding problems and candidiasis (24,25).

It has been shown that the use of fluoroquinolones and ciprofloxacin in particular, the most commonly used member of this group, causes arthropathy in newborn animals. In addition, this group of drugs may cause green teeth and pseudomembranous colitis. Thus, fluoroquinolones should be avoided as first-line treatment in breastfeeding women (26). Cotrimoxazole (trimethoprim/sulfamethoxazole) should not be

Table 3. Drugs used in dental treatment in puerperal period-modified from Suresh and Radfar (3)

Analgesics	Usability during the puerperal period
Acetaminophen	Yes
Aspirin	No
Ibuprofen	Yes
Naproxen	Yes
Codeine	Yes
Oxycodone	With caution
Hydrocodone	With caution
Morphine	Yes
Propoxyphene	Yes
Meperidine	Yes
Pentazocine	With caution
Antibiotics	
Amoxicillin	Yes
Metronidazole	Yes
Erythromycin	Yes
Penicillin V	Yes
Cephalosporins	Yes
Gentamycin	Yes
Clindamycin	Yes
Tetracycline	No
Chloramphenicol	No
Chlorhexidine	No data
Azithromycin	Yes
Antifungals	
Nystatin	Yes
Clotrimazole	Yes
Fluconazole	With caution
Ketoconazole	No
Local anesthetics	
Lidocaine	Yes
Mepivacaine	Yes
Prilocaine	Yes
Bupivacaine	Yes
Etidocaine	Yes
Corticosteroids	
Prednisolone	Yes
Sedative/hypnotics	
Nitrous oxide	Yes
Barbiturate	No
Benzodiazepines	No

used in babies younger than two months and nursing mothers of these babies due to the risk of kernicterus.

The antibiotics that pass into breast milk at the highest rates are sulfapyridine, vancomycin, linezolid, metronidazole, and ciprofloxacin. Besides, antibiotics that pass into breast milk at a minimum rate are cefoperazone, sulbenicillin, benzylpenicillin, clarithromycin, and cefotaxime. The two antibiotics with the highest ratio of absolute infant dose/therapeutic infant dose, are metronidazole and vancomycin. Therefore, whether these antibiotics will be used or not should be decided by considering the benefit/harm ratio (27-29). Azithromycin is also one of the antibiotics preferred for use in the puerperium because it passes into breast milk at low levels and can be used at relatively high doses in neonates, it would not be expected to cause adverse effects in breastfed infants. A cohort study reported that hypertrophic pyloric stenosis was up to three times more common in breastfed infants of mothers using macrolide antibiotics. However, since this study used mostly erythromycin and azithromycin in only 7% of cases, the authors could not make a definitive prediction about which macrolides caused this increased risk (20,30).

Analgesics

Ibuprofen can be used as an analgesic in infants with doses up to 40 mg/kg/day. However, the dosage of ibuprofen the infant takes through breastfeeding is approximately 68 mcg/kg/day as ibuprofen has a breast milk excretion rate of 0.38%. Ibuprofen is the drug of choice among the non-steroidal anti-inflammatory drugs during breastfeeding since the total dose an infant receives through breastfeeding is far below the maximum pediatric dosage limit (23).

In cases where an anti-inflammatory effect is not required, paracetamol may be preferred as an analgesic in the first-line (29). The rate of paracetamol excretion into breast milk in maternal use is approximately 0.04-0.23%. The time for this drug to reach the peak amount in breast milk is approximately one hour and its half-life is 2.7 hours. There are no reported adverse effects in babies related to the usage of paracetamol in nursing mothers (26). Paracetamol becomes undetectable in the blood (<0.5 mg/L) 12 hours after the dose is administered. However, paracetamol should be used more carefully, mainly in breastfeeding mothers whose babies are born prematurely, born with low birth weight, or have severe medical conditions. It should also be noted that there are preparations of paracetamol combined with codeine on the market. Paracetamol preparations in combination with codeine or similar drugs should not be used during the breastfeeding period (31).

Methimazole (dipyrone) is not used in North America and some European countries due to its severe side effects, such as agranulocytosis. Therefore, information about the safety of this

compound in women who are breastfeeding is limited. The European Medicines Agency banned the use of methimazole in the last trimester of pregnancy and during breastfeeding with a regulation issued in 2018 (32).

Acetylsalicylic acid (aspirin) usage in high doses during lactation may cause adverse effects, such as thrombocytopenic purpura, metabolic acidosis, or gastrointestinal tract bleeding in the infant, so it is not considered safe. While the American Academy of Pediatrics recommends the use of aspirin with caution, the British Medical Association recommends against its use during breastfeeding due to the risk of Reye's syndrome (33). On the other hand, there are studies reporting that low dose (85-100 mg/day) use of aspirin is safe for the infant (34).

Antiseptics and oral rinsing solutions

Transient hypothyroidism may occur in the newborn due to the frequent or liberal use of povidone-iodine solutions close to birth and during breastfeeding. This adverse effect is more commonly encountered in countries and regions with endemic iodine deficiency. Although povidone-iodine solutions are absorbed in small amounts through intact adult human skin, it is absorbed from skin wounds, and oral and vaginal mucosa much more easily. Therefore, it should not be applied to large surface areas and for a long time, and repeated administrations should be avoided (35,36).

No toxicity associated with the maternal use of chlorhexidine solutions has been reported in breastfed infants. Its topical use in breast cleansing, especially before and after breastfeeding, and its usage in oral rinsing in the mother did not appear to adversely affect the breastfed infants (20).

Local anesthetics

Lidocaine passes into breast milk at a low rate, even after high doses are administered as a local anesthetic. At the same time, lidocaine is poorly absorbed by the infant's gastrointestinal tract. Therefore, maternal use of lidocaine as a local anesthetic is not expected to cause adverse effects in breastfed infants and no specific precautions are required (37,38).

Recommendations for maintaining oral health

Frequent dental check-ups and continuous evaluation of the patient's functional status are necessary to determine new treatment and recommendation needs. Unfortunately, it is not always possible for these check-ups to be performed frequently. Recommendations to be made for the maintenance of oral health of the puerperal patient can be examined in two parts; home care and nutritional guidance.

Home care to support clinical treatment is of the utmost importance in these cases. Examples of home applications for care and protection are basic oral hygiene practices, antimicrobial gels, toothpaste, dental floss applications, carbonated water or mouthwashes, and sugar-free gums. Electric toothbrushes may also be recommended in this context.

Regular toothbrushing with fluoride toothpaste is the principal, non-professional intervention to prevent caries (39). In one study, sodium fluoride added to water was shown to pass into breast milk and have a detrimental effect on learning and memory in mouse pups (40). However, this study was conducted with high doses of fluoride (100 mg/L). This dose is well above the dose accepted by the Food & Drug Administration to be found in toothpastes (41,42). No human studies were found on the effect of fluoride transferred from breastmilk via maternal toothbrushing to the infant.

Periodontal diseases may negatively impact oral health-related quality of life (OHRQoL) of puerpera. Most studies assessing the impact of periodontal diseases on OHRQoL of pregnant women use clinical assessments, such as probing depth and clinical attachment loss to examine the periodontal status. This can be challenging and time-consuming to perform, especially for new breastfeeding mothers early postpartum (4,6). Therefore, plaque elimination by the dentist and strict adherence by the patient to their own oral hygiene procedures are needed to support periodontal health.

Another issue to be considered in the puerperal period is nutrition. The major cause of tooth decay is sugary foods that may easily stick to the teeth. Therefore, consumption of foods containing plenty of sugar or carbohydrates between meals should be avoided. It has been reported that drugs used for various reasons during this period, especially drugs in the form of syrup, contributed to the formation of caries due to their sweetener content. In these cases, rinsing the mouth with water following the use of the drug is an appropriate preventive practice.

Although their use is not very common during this period, some drugs, such as antihistamines, antidepressants, diuretics and psychotherapeutics, may cause a decrease in saliva secretion. Furthermore, salivary secretion may decrease due to dysfunction of the salivary glands in cases with hypertension, diabetes, or chronic depression. Thus, a tendency to caries formation occurs. In these cases, sugar-free chewing gum, carbonated mouthwash, and artificial saliva preparations can be used to relieve dry mouth, or water and other liquids may be recommended to be consumed abundantly and frequently (15-17).

Conclusion

Oral care is an integral part of overall health for women in the postpartum period, as it is for every individual. The puerperal period is more important than other times since oral and dental

care severely affects general health when neglected. If good oral hygiene is provided for these patients, their general health and their quality of life will be maintained or even improve. Oral health awareness should not be neglected in women who are in the postpartum period. At the same time, there is a need for special training for dentists and allied health professionals who will provide the oral health services to postpartum patients.

Footnotes

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Pustular psoriasis of pregnancy with paradoxical facial involvement: an uncommon presentation-what is your diagnosis?

A 30-year-old primigravida with a gestation period of 34 weeks presented to the dermatology outpatient department with multiple, painful and mildly pruritic, pus-filled lesions of two weeks duration associated with mild fever. The lesions initially started over the chest area as an erythematous rash, followed by development of pustules and then spread rapidly to involve the entire trunk, and upper and lower limbs within five days. There was no history of prior psoriatic lesions. She was not taking any medication except for iron and folic acid. On clinical examination, her vitals were stable. Cutaneous examination revealed erythematous plaques with superimposed pustules over the entire abdomen, trunk, and upper and lower extremities (Figure 1). Her face was also involved, with multiple pustules over the forehead, cheeks and chin. Erythematous plaques with tiny pustules along the margins were seen in both the periorbital areas (Figure 2). Old lesions showed desquamation and scaling. Palms, soles and oral cavity were normal. Obstetric examination showed fundal height consistent with 32 weeks gestation with fetus in cephalic presentation and normal liquor. The patient was admitted under the Dermatology department, with obstetric team taking care of fetal surveillance. Complete blood count showed neutrophilic leukocytosis (10,800/mm^3), low-albumin (2.9 g/dL) and raised erythrocyte sedimentation rate (60 mm/hr). Other laboratory investigations, including corrected calcium, blood sugar, renal and liver function tests, and serum

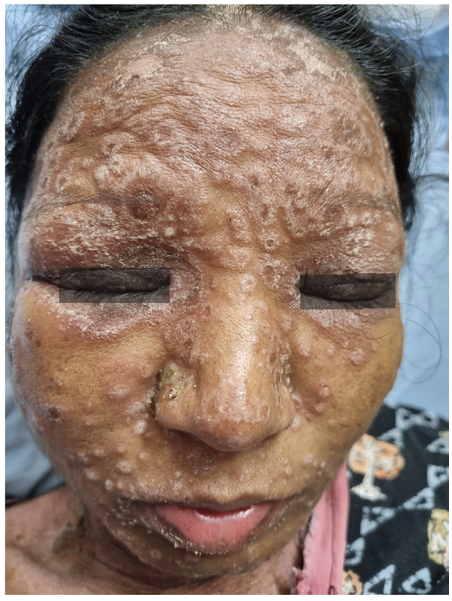

Figure 1. Multiple erythematous plaques with superimposed pustules over entire abdomen, old pustules over upper abdomen showing desquamation

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electrolytes were within normal limits. Swabs from the pustules were sterile and showed no growth. Skin biopsy from an involved area showed intracorneal and sub-corneal pustule formation with marked neutrophilic infiltrate. The epidermis also showed hypogranulosis, focal parakeratosis, and irregular acanthosis with mild supra-papillary thinning at places. The superficial dermis showed few dilated capillaries, and perivascular inflammation comprised of neutrophils and a few lymphocytes confirming the diagnosis of pustular psoriasis of pregnancy (PPP) (Figure 3).

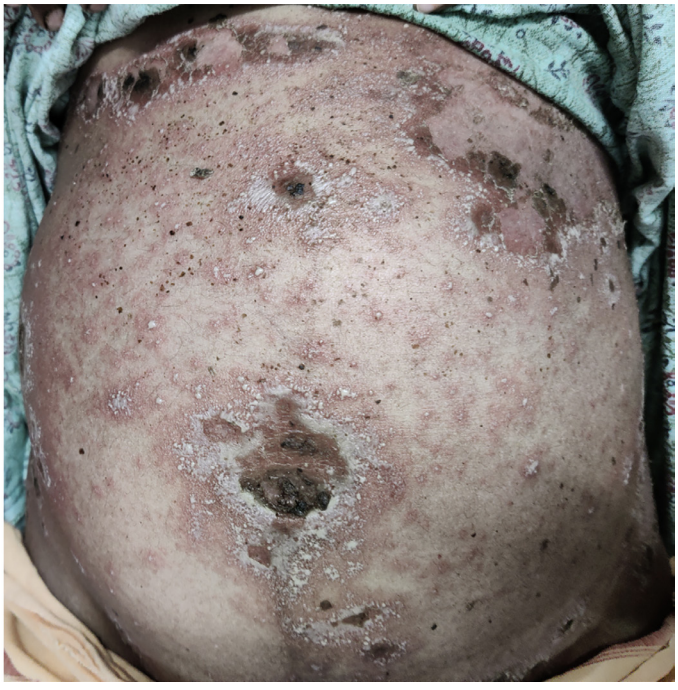

Figure 2. Multiple pustules arranged in annular pattern over underlying erythema over forehead, cheeks, chin and peri-orbital areas

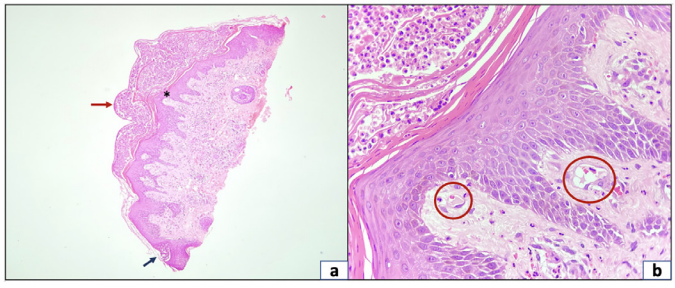

Figure 3. (a) Low power view showing intra-corneal (red-arrow) and sub-corneal (black-arrow) pustule formation, irregular acanthosis, elongated rete-pegs and focal thinning of supra-papillary epidermal plates (asterisk); (b) Higher magnification showing neutrophilic content of the intra-corneal pustule, underlying parakeratosis, hypogranulosis, mild spongiosis, and dilated capillaries in the papillary dermis (circled)

The patient was started on oral prednisolone 60 mg along with protein supplementation. Initially lesions subsided but after the third day new eruptions of pustules developed and showed no improvement even after one week. So, she was started on oral cyclosporine 150 mg (3 mg/kg/day) per day with regular monitoring of blood pressure, renal parameters, and serum electrolytes. Due to the risk of utero-placental insufficiency in PPP, she was kept on strict antepartum surveillance with weekly Doppler and non-stress test. Lesions started desquamating on day two and there was complete resolution of the lesions by the tenth day. However, on tapering the cyclosporine dose, she developed new pustules. So, she was maintained on 150 mg of cyclosporine until 38 weeks of pregnancy. Labor was induced at 38 weeks and she delivered a healthy female child with birth weight 2260 grams. After delivery, cyclosporine was tapered and stopped over a period of five weeks. The patient was reviewed one month after stopping cyclosporine and there were no new pustules.

Answer

PPP, previously known as impetigo herpetiformis (IH), is a rare, severe pregnancy dermatosis that carries a bad prognosis for both the mother and the baby if left untreated. In 1872, Von Hebra et al. (1) first coined the incorrect name IH after reporting five pregnant women with inflammatory clustered pustular lesions with five fetal and four maternal deaths. Later, in 1910, Leo Ritter von Zumbusch (1874-1940), an Austrian dermatologist and professor from Vienna, first described the term, generalized pustular psoriasis (GPP) (2). Currently, the term IH is unfavored and is being replaced by the term PPP by many authors as it is most likely to be a variation of GPP that flares up in response to a variety of triggers present in pregnancy. These include metabolic disturbances, systemic steroid withdrawal, and pregnancy itself. PPP is also considered to be a dermatosis of pregnancy owing to the importance of early recognition and treatment (3).

The exact pathophysiology of PPP is not currently known. Pathogenic mutations in the interleukin 36 receptor antagonist (IL36RN) gene, personal or family history of psoriasis, low serum vitamin D, increasing levels of progesterone during the last trimester of pregnancy, hypocalcaemia, and disruption in elastase activity are some of the factors known to be associated with PPP (3). PPP usually occurs in the third trimester of pregnancy, as in the described case, owing to increased progesterone levels. However, it has also been reported to occur during first trimester and postpartum. PPP is also known to recur in a significant proportion of subsequent pregnancies and that too at an early period (4). Clinically, PPP is characterized by erythematous plaques with pustules along the margins. The lesions initially develop in skin folds and then gradually spread

centrifugally to involve the entire body. The face, palms and soles are typically spared with occasional involvement of oral mucosae. Our patient had atypical involvement of her face. Skin lesions are usually associated with systemic features, including fever, myalgia and malaise (2).

The lesions of PPP are known to resolve spontaneously after parturition. However, it can result in life threatening complications if not treated and monitored properly during pregnancy. Various complications include cardiovascular failure, severe respiratory distress syndrome, hypocalcemia seizures, tetany, hypoalbuminemia, delirium in the mother and placental insufficiency, intrauterine growth restriction, premature rupture of membranes, miscarriage, fetal abnormalities, and stillbirth in the baby (3). Differential diagnoses of PPP include pustular psoriasis, acute generalized exanthematous pustulosis, sub-corneal pustular dermatosis, gestational pemphigoid, and atopic eruption of pregnancy (5).

Aggressive treatment and close monitoring of the mother and fetus are vital in the management of women with PPP. Oral corticosteroid, especially prednisolone, is considered to be the first choice of drug in mild cases of PPP. The dose of prednisolone can vary from 30 mg to 80 mg depending upon the response. However; in cases resistant to steroid and in severe cases, oral cyclosporine at a dose of 3-5 mg/kg/day has become the accepted therapy. Moreover, the efficacy of cyclosporine is enhanced when combined with oral prednisolone. Biological agents like infliximab and secukinumab, and narrow band ultraviolet-B have also been used to treat PPP (2,4,6).

Thus, we present an atypical case of PPP with a rare distinguishing feature of severe facial involvement in the form of pustules and erythematous plaques with pustules at the margin in the periorbital areas.

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Ethics

Informed Consent: *Informed consent was obtained from the patient for the publication of case details and associated images.*

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Manual reduction in conjunction with Arabin pessary to reduce first trimester urinary retention relapse

To the Editor,

We present our experience of acute urinary retention in the first trimester, solved through manual reduction and subsequent Arabin pessary placement with the aim of highlighting what we believe to be a useful approach. Moreover, to the best of our knowledge, few inconclusive data have previously been reported about Arabin pessary use to reduce recurrent urinary retention after manual reduction of retroverted uteri.

Case 1: A 35 years old, Gravida 2 Para 1 at 13.5 weeks. Attended emergency room for pelvic pain. A bladder globe, correlated to an obstructed urination for a retroverted uterus was detected. There was no sonographic sign of uterine incarceration. The patient was catheterized (800 cc of urine) and discharged after education to reduce urinary retention. Urine culture was negative. Five days later she presented again with a globe of 750 cc of urine. The cervix was cranialized on transabdominal ultrasound (Figure 1A). Therefore, a manual reduction of retroverted uterus was performed under sedation without complication. Subsequently, an Arabin pessary was placed (Figure 1B). The patient voided spontaneously after the procedure, with negative post-micturition residues. Some days later the patient presented because of a spontaneous expulsion of the pessary. However, she also had a retroposed cervix and no urinary retention at this time. The follow-up at 16 weeks was negative, with normal reported urinary voiding, and negative post-micturition residue. The cervix was posteriorized, even in absence of the pessary (Figure 1C).

Case 2: A 35 years old, Gravida 2 Para 1 at 13.1 weeks. Attended because of complete inability to urinate. She presented with a urinary globe correlated to a retroverted uterus. During three evaluations, spaced three-four hours apart, to monitor the ability for spontaneous urination, she underwent three bladder catheterizations, respectively of 1200, 1100 and 1000 cc. Ultrasound scan excluded uterine incarceration and reported a cranialized and retropubic cervix. Urine culture was negative. A manual reduction of the retroverted uterus was performed under sedation without complication. After the manoeuvre, an Arabin pessary was placed to maintain the modified angle of the cervix. The patient voided spontaneously after the procedure, with negative post-micturition residues. The follow-up at 16.6 weeks was negative, with a negative urine culture (Figure 1D). After Arabin removal, the cervix remained posterior (Figure 1E), and the patient regularly and spontaneously voided, with a negative post-micturition residue.

In both cases, the subsequent pregnancy controls were regular, and he patients reported no more acute urinary retention.

Acute urinary retention, defined as failure to willingly empty a bladder filled by over 200 mL of urine, occurs in between 1:3000-1:8000 pregnancies, typically before 16 weeks of gestation (1). This rare occurrence has also been associated with incarcerate uteri. A non-incarcerated retroverted uterus is an uncommon cause of inability to void urine (2), due to mechanical compression on the lower bladder by the anteriorly and superiorly displacing uterine cervix and to the increase in the vesical - urethral angle (3,4).

Urinary catheter or intermittent bladder catheterization are possible approaches. However, these procedures are reported to cause patient discomfort and a higher risk of urinary infections. The patients' education (adequate position during urination, adequate hydration, periodic urination at pre-established time) is the first strategy to reduce urinary retention (5).

A manual reduction of retroverted uteri was reported to be a valid option. The repositioning of the uterus in an anterior

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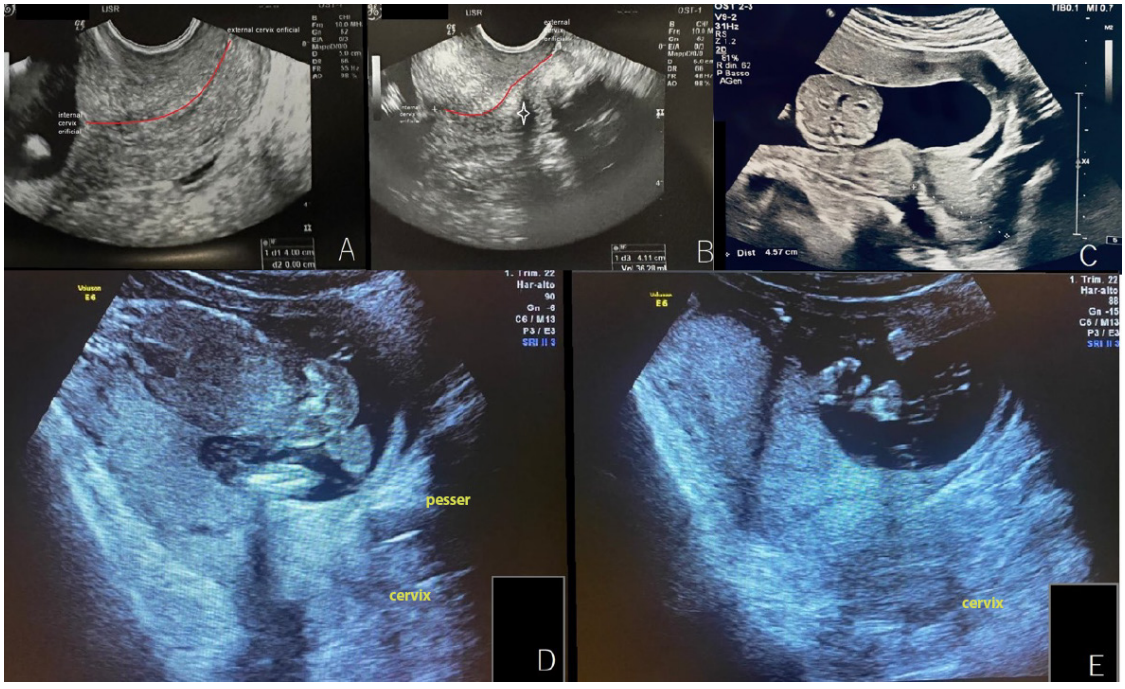

Figure 1. Case 1: (A) Under the pubic region and cervix of the patient, at first hospital attendance; (B) Modified angle of cervix after pessary placement. The acoustic shadow of the pessary is highlighted with a white star while the direction of the cervix is indicated with a red line; (C) Ultrasound visualization of the retroposed cervix at 16-week follow-up. Case 2: (D) Ultrasound visualization of Arabin pessary at routine follow-up visit; (E) A persistent retroposed cervix after pessary removal

position, in which the bladder is decompressed, may be performed by first putting the patient in the dorsal lithotomy position, under local or general anaesthesia. Then two fingers should be inserted into the vagina along the posterior fornix. With simultaneous pressure on the suprapubic abdominal wall, a sudden loss of resistance is obtained as the uterus is repositioned into its anterior location (5-7). A gentle and slow pressure will prevent placenta detachment or premature rupture of the membrane (5). Some authors propose manual subsequent vaginal ring positioning until 20 weeks gestation (5). Arabin placement is a well-accepted and minimally invasive procedure, but not yet validated as a therapy for urinary retention. However, few data are reported about Arabin pessary in this clinical situation (8,9). Even if its use seems to be beneficial and it is a minimally invasive and relatively simple and complication-free, the use of Arabin pessary to prevent a relapse is not widely recognized. In particular, in the presented cases, even if the patients presented with similar characteristics, one retained and one spontaneously expelled the Arabin pessary, although the eventual outcomes were similar. A possible explanation for this difference may be that after a few days in the posteriorized position, the cervix maintained its placement without Arabin. It may be of interest to evaluate the minimum time to achieve a cervical posterior placement.

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The challenge of diagnosing tubo-ovarian abscess and the necessity for aggressive management

To the Editor,

We are writing to address a critical issue in the management of tubo-ovarian abscesses (TOA), highlighted by two recent cases treated at our facilities. These cases illustrate the diagnostic difficulties and the urgent need for aggressive management to avoid potentially fatal complications associated with TOA.

TOA is a severe complication of pelvic inflammatory disease (PID). However, the term PID can be confusing, as it encompasses a spectrum of conditions ranging from milder presentations to more severe forms. To avoid misunderstandings and underdiagnosis, it would be prudent to use more specific terms, such as endometritis, salpingitis, tubal abscess, and TOA. This distinction is important because TOA itself poses significant life-threatening risks. Moreover, the most important consideration in cases of PID is to exclude the possibility of a TOA, given its severity and the necessity for hospitalization. An undiagnosed TOA presents a high risk of rupture and necessitates emergency surgery, highlighting the need for accurate and timely diagnosis (1).

In stable patients with few symptoms, a medical approach may be considered, with prompt and "aggressive" initiation of broad-spectrum antibiotic therapy within the "golden hour". In cases of large abscesses (≥6 cm) or lack of clinical response within 48-72 hours, surgical treatment is mandatory to reduce the risk of TOA rupture.

While ultrasound can be helpful, it is often inadequate for diagnosing TOA due to its limitations in visualizing the ovary alongside an abscessed tube, making diagnosis challenging (2).

In our first case, a 44-year-old woman presented with abdominal pain and fever. Her personal history was unremarkable, and she used an intrauterine device (IUD) for contraception. Initial transvaginal and transabdominal ultrasound findings were inconclusive, showing only a "functional cyst" and minimal free fluid. Forty-eight hours later, her condition worsened, and a computed tomography (CT) scan ultimately revealed a left adnexal abscess. The patient required urgent laparoscopic surgery, during which a left adnexectomy and IUD removal were performed. Postoperative complications included pleural effusion and pulmonary empyema, highlighting the severe and rapidly evolving nature of TOA (3). After intensive care unit hospitalization and broad-spectrum antibiotics, the patient recovered.

Our second case involved a 36-year-old, obese woman with a history of IUD use, who presented with fever and pelvic pain. Initial evaluations, including ultrasound, did not yield conclusive findings. However, worsening symptoms and fever led to a CT scan three days later, which confirmed a TOA. Despite aggressive antibiotic treatment, the patient's clinical condition worsened, with coincident development of lobar pneumonia, illustrating the necessity of prompt and comprehensive treatment for TOA (4). The patient underwent laparotomy with removal of the left TOA, and of the IUD simultaneously. Hospitalization in the intensive care unit was required, where antibiotic therapy was continued, and the clinical condition improved.

These cases emphasize the importance of a systematic diagnostic approach. Detailed patient history, clinical examination, and advanced imaging, such as CT and pre-surgical chest X-rays, are critical for accurate diagnosis and management of TOA (5). The rapid progression of TOA necessitates early and aggressive treatment with broad-spectrum antibiotics targeting anaerobes, including

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Bacteroides fragilis, and timely surgical intervention when indicated.

A multidisciplinary approach in the management of TOA is mandatory. Prior to progression to septic shock, collaboration between the gynecologist, microbiologist, and infectious disease specialist is essential for enabling conservative medical management. If septic shock develops, the support of anesthesiologists and intensive care specialists is necessary to manage the severe clinical condition of the patients.

The diagnosis and management of TOA requires a high level of clinical suspicion and a multi-faceted approach. Clinicians should be vigilant for signs of TOA, use advanced imaging techniques, and be prepared for aggressive treatment strategies to address this serious condition effectively.

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DOI: 10.4274/jtgga.galenos.2025.e001

Retraction notice: "*Relation between single serum progesterone assay and viability of the first trimester pregnancy"* by Abdelazim IA, Belal MM, Makhlouf HH published in J Turk Ger Gynecol Assoc. 2013 Jun 1;14(2):68-71. doi: 10.5152/jtgga.2013.09471 (1).

The Editors have retracted this article. This decision follows a detailed investigation prompted by allegations raised by a third party. The investigation revealed that the data presented in this article were previously published in two other scientific journals by the same authors (2,3). As a result, the conclusions drawn in this article are deemed invalid. The corresponding author has agreed with the decision to retract the article.

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DOI: 10.4274/jtgga.galenos.2025.e002

Retraction notice: "*The role of magnetic resonance imaging in refining the diagnosis of suspected fetal renal anomalie"* by Abdelazim IA and Belal MM published in J Turk Ger Gynecol Assoc. 2013 Mar 1;14(1):6-10. doi: 10.5152/jtgga.2013.02 (1).

The Editors have retracted this article. This decision follows a detailed investigation prompted by allegations raised by a third party. The investigation revealed that the data presented in this article were previously published in another scientific journal by the same authors (2). As a result, the conclusions drawn in this article are deemed invalid. The corresponding author has agreed with the decision to retract the article.

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Retraction notice: "*Relationship between uterine natural killer cells and unexplained repeated miscarriage"* by Farghali MM, El-kholy AG, Swidan KH, Abdelazim IA, Rashed AR, El-Sobky E, and Goma MF published in J Turk Ger Gynecol Assoc. 2015 Dec 1;16(4):214-218. doi: 10.5152/jtgga.2015.0082 (1).

The Editors have retracted this Article. This decision was made following an investigation prompted by allegations raised by a third party. The Editorial Board identified unusual features in some of the reported data and requested the authors to provide the raw datasets for verification. However, the authors were unable to supply the original files. Consequently, the Editorial Board has lost confidence in the validity of the article's conclusions.

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DOI: 10.4274/jtgga.galenos.2025.e004

Retraction notice: "*Maternal and obstetrical factors associated with a successful trial of vaginal birth after cesarean section*" by Abdelazim İA, AAME, Al-Kadi M, Yehia AH, Nusair BMS, and Faza MA published in J Turk Ger Gynecol Assoc. 2014 Dec;15(4):245-249. doi: 10.5152/jtgga.2014.14104 (1).

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DOI: 10.4274/jtgga.galenos.2025.e005

Retraction notice: "*Accuracy of three-dimensional multislice view Doppler in diagnosis of morbid adherent placenta"* by Moniem AMA, Ibrahim A, Akl SA, Aboul-Enen L, and Abdelazim IA published in J Turk Ger Gynecol Assoc. 2015 Sep;16(3):126-136. doi: 10.5152/jtgga.2015.15038 (1).

The Editors have retracted this Article. This decision was made following an investigation prompted by allegations raised by a third party. The Editorial Board identified unusual features in some of the reported data and requested the authors to provide the raw datasets for verification. However, the authors were unable to supply the original files. Consequently, the Editorial Board has lost confidence in the validity of the article's conclusions.

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DOI: 10.4274/jtgga.galenos.2025.e006

Retraction notice: "*Pipelle endometrial sampling versus conventional dilatation & curettage in patients with abnormal uterine bleeding"* by Abdelazim IA, Aboelezz A, and Abdulkareem AF published in J Turk Ger Gynecol Assoc. 2013 Mar 1;14(1):1-5. doi: 10.5152/jtgga.2013.01 (1).

The Editors have retracted this Article. This decision was made following an investigation prompted by allegations raised by a third party. It has come to attention that a methodological counterpart of this article was published in another journal shortly thereafter, with overlapping patient recruitment periods between the two studies (2). The Editorial Board requested the authors to provide the raw datasets for verification. However, the authors were unable to supply the original files. Consequently, considering the detection of other duplication cases by the corresponding author, the Editorial Board has lost confidence in the validity of the article's conclusions.

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CONGRESS CALENDER

INTERNATIONAL MEETINGS

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

March 25-29, 2025	Society for Reproductive Investigation (SRI) 72nd Annual Scientific Meeting, North Carolina, USA
April 24-26, 2025	11th Congress of the Society of Endometriosis and Uterine Disorders (SEUD), Prague, Czech Republic
April 23-27, 2025	**XV. Türk Alman Jinekoloji Kongresi, Antalya, Türkiye**
April 24-26, 2025	ASCCP 2025 Scientific Meeting, San Diego, USA
May 14-16, 2025	15th European Congress on Menopause and Andropause, Valencia, Spain
May 16-18, 2025	American College of Obstetricians and Gynecologists (ACOG) 2025 Annual Clinical and Scientific Meeting, Minneapolis, USA
May 17-21, 2025	American Society for Reproductive Immunology (ASRI) Annual Meeting 2025, Minnesota, USA
June 17-20, 2025	The Society of Obstetricians and Gynecologists of Canada Annual Clinical Scientific Conference, Whistler, BC, Canada
June 18-21, 2025	International Urogynecological Association (IUGA) 50th Annual Meeting, Barcelona, Spain
June 29-July 02, 2025	European Society of Human Reproduction and Embryology (ESHRE) 41st Annual Meeting, Paris, France
September 14-17, 2025	35th ISUOG World Congress, Cancun, Mexico
October 25-29, 2025	American Society for Reproductive Medicine (ASRM) 81st Annual Meeting, Texas, USA
October 19-22, 2025	ESGE 34th Annual Congress, İstanbul, Türkiye
November 08-11, 2025	The 54th American Association of Gynecologic Laparoscopists (AAGL) Global Congress on Minimally Invasive Gynecologic Surgery (MIGS), Vancouver, BC, Canada
November 27-29, 2025	The 33rd World Congress on Controversies in Obstetrics Gynecology & Infertility (COGI), Rome, Italy

CONGRESS CALENDER

NATIONAL MEETINGS

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

April 03-06, 2025	18. Uludağ Jinekoloji ve Obstetrik Kış Kongresi, Bursa, Türkiye
April 23-27, 2025	**XV. Türk Alman Jinekoloji Kongresi, Antalya, Türkiye**
May 14-18, 2025	22. Ulusal Jinekoloji ve Obstetrik Kongresi, K.K.T.C.
May 15-19, 2025	4. Uluslararası Pelvik Taban ve Kozmetik Jinekoloji Kongresi, Antalya, Türkiye
May 23-24, 2025	Minimal İnvaziv Jinekolojik Cerrahi Sempozyumu, Ankara, Türkiye
September 11-14, 2025	Uludağ Jinekolojik Endoskopi Kampı, Bursa, Türkiye
September 18-21, 2025	İç Anadolu Kadın Sağlığı Derneği Kongresi, Ankara, Türkiye
September 25-28, 2025	4. Tüp Bebek ve İnfertilite Derneği Kongresi, K.K.T.C.
October 01-05, 2025	7. Jinekoloji ve Obstetrikte Tartışmalı Konular Kongresi, Antalya, Türkiye
October 29-November 01, 2025	Türkiye Maternal Fetal Tıp ve Perinatoloji Derneği Ultrasonografi Kongresi, İstanbul, Türkiye
October 29-November 02, 2025	12. Üreme Tıbbı ve Cerrahisi Derneği Kongresi, Antalya, Türkiye
November 06-09, 2025	Uluslararası Jinekoloji ve Obstetri Kongresi (UJOK), Antalya, Türkiye
November 20-23, 2025	13. Üreme Sağlığı ve İnfertilite Kongresi, Antalya, Türkiye
February 12-15, 2026	8. Minimal İnvaziv Jinekolojik Cerrahi Kongresi, Ankara, Türkiye