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CONTENTS

ORIGINAL ARTICLES

REVIEWS

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Impact of dienogest therapy on CA125 levels, hormonal profile, and systemic inflammatory indices in endometriosis

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ABSTRACT

Aims: The present study aims to evaluate the impact of dienogest therapy on CA125 levels, hormonal profile, and systemic inflammatory indices in patients with endometriosis, a chronic inflammatory disorder in which inflammation constitutes a fundamental component of the pathophysiology.

Methods: This retrospective, pre–post analytical study included 150 female with endometriosis who received dienogest. Demographic and laboratory data were obtained from electronic medical records. Systemic inflammatory indices including neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), neutrophil-to-monocyte ratio (NMR), platelet-to-lymphocyte ratio (PLR), mean platelet volume (MPV), MPV-to-lymphocyte ratio (MPVLR), cancer antigen 125 (CA-125), Systemic Immune-inflammation Index (SII), Systemic Inflammation Response Index (SIRI), and pan-immune-inflammation value (PIV) were evaluated before and after treatment. Statistical analyses were performed using appropriate parametric and nonparametric tests, and correlation analyses were conducted.

Results: Following dienogest therapy, statistically significant reductions were observed in CA125 levels ($p=0.010$) and PLR ($p=0.028$), along with decreases in leukocyte, and PCT levels. FSH levels showed a significant increase ($p=0.001$), whereas LH, estradiol, progesterone, TSH, FT3, and FT4 levels remained unchanged ($p>0.05$ for all). Significant increases were also noted in hemoglobin, hematocrit, MCV, and MCH values after treatment ($p<0.05$). No statistically significant differences were detected in NLR, MLR, NMR, MPVLR, SII, SIRI, or PIV. Correlation analyses demonstrated a positive association between CA 125 and PLR, as well as inverse correlations between CA125 and hematocrit.

Conclusion: Dienogest therapy was associated with a reduction in CA125 levels and specific inflammatory markers, alongside improvements in certain hematological parameters in patients with endometriosis. These findings suggest a potential anti-inflammatory benefit, indicating that dienogest may be involved in the modulation of systemic inflammatory burden. Furthermore, the preservation of endocrine homeostasis may support its favorable safety profile as an effective therapeutic option in the management of endometriosis.

Keywords: Endometriosis, dienogest, CA125, systemic inflammation, hematological parameters

INTRODUCTION

Endometriosis is defined as the presence of endometrial glandular and stromal lesions localized outside the uterine cavity.[1,2] These lesions manifest phenotypically as peritoneal implants, superficial ovarian endometriosis, endometriomas, or deep infiltrating endometriosis. Although the precise etiology of endometriosis remains to be fully elucidated, several hypotheses have been proposed to explain the development of endometriotic lesions. The most widely accepted mechanisms include retrograde menstruation, Müllerian remnants that fail to undergo appropriate differentiation or migration during fetal development, and transdifferentiation of circulating blood cells into endometriotic tissue.[3,4] Inflammation plays a pivotal role in the pathophysiology of endometriosis. It has been demonstrated that inflammatory processes lead to the upregulation of key components of signaling pathways, such as mitogen-activated protein kinase (MAPK), which may constitute a potential therapeutic target in endometriosis.[1,5] In this context, dienogest, a synthetic progestin with well-established anti-inflammatory and anti-proliferative properties, is widely used in the management of endometriosis.[6]

Experimental animal models and in vitro cell culture studies have demonstrated that dienogest markedly suppresses the viability and proliferation of endometrial stromal cells stimulated by pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-32. This reduction was accompanied

by decreased expression of proliferating cell nuclear antigen and diminished phosphorylation of protein kinase B (AKT), indicating suppression of inflammatory signaling pathways.[7] Furthermore, another study demonstrated that dienogest downregulates the expression of inflammatory and neuroangiogenic mediators, such as cyclooxygenase-2 (COX-2), IL-6, IL-8, and vascular endothelial growth factor (VEGF), via progesterone receptor isoforms, thereby further supporting its anti-inflammatory effects.[8]

Systemic inflammatory indices have been extensively investigated in a broad spectrum of clinical disorders, including polycystic ovary syndrome (PCOS), hypertension, and diabetes mellitus.[9,10] However, there remains a notable paucity of studies evaluating the impact of dienogest on systemic inflammatory indices, including neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), neutrophil-to-monocyte ratio (NMR), platelet-to-lymphocyte ratio (PLR), mean platelet volume (MPV), MPV-to-lymphocyte ratio (MPVLR), cancer antigen 125 (CA-125), Systemic Immune-inflammation Index (SII), Systemic Inflammation Response Index (SIRI), and pan-immune-inflammation value (PIV) in patients with endometriosis.

Accordingly, the present study aimed to comprehensively evaluate systemic inflammatory indices, including NLR, MLR, PLR, NMR, MPV, MPVLR, CA-125, SII, SIRI, and PIV, in patients with endometriosis/endometrioma, a disorder in which inflammation constitutes a central component of its underlying etiology.

METHODS

All necessary ethical approvals for this retrospective study were obtained from the Ethics Committee for Non-interventional Researches at Kırıkkale University (Date: 16.10.2024, Decision No: 2024.10.01). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Protocol

This study was designed as a single-center, retrospective observational pre–post (paired) analytical study. Patients who were followed with a diagnosis of endometriosis at the Department of Obstetrics and Gynecology, Faculty of Medicine, Kırıkkale University, between January 2018 and September 2024. The study included patients treated with a daily 2 mg dose of dienogest for a mean duration of six months. Blood samples were collected on days 2-3 of the menstrual cycle to ensure standardized hormonal assessment. Patients diagnosed with endometriosis based on histopathological findings and those with ultrasonographic evidence of endometrioma were selected.

Demographic variables, including sex and age, along with laboratory parameters (e.g., complete blood count and biochemical profiles), were extracted from the hospital's electronic medical records. Based on these data, systemic inflammatory indices including NLR, MLR, NMR, PLR, MPV, MPVLR, SII, SIRI, and PIV were assessed before and after dienogest therapy in 150 female with endometriosis aged 18-50 years.

Inclusion Criteria

Participants were eligible for inclusion if they had a diagnosis of endometriosis or endometrioma confirmed by clinical and histopathological findings, had no history of chronic inflammatory disease, malignancy, or pregnancy, and had not used medications that could influence inflammatory status, including oral contraceptives, steroid hormones, insulin sensitizing agents, or anti inflammatory drugs, within the preceding six months.

Exclusion Criteria

Participants were excluded if they did not meet the diagnostic criteria for endometriosis or endometrioma based on clinical and histopathological findings, had a history of chronic inflammatory disease, malignancy, or pregnancy, had used medications that could affect inflammatory status, including oral contraceptives, steroid hormones, insulin sensitizing agents, or anti inflammatory drugs, within the preceding six months, or were younger than 18 years of age.

Statistical Analysis

The data analyses were performed using IBM SPSS Statistics for Windows (version 27.0; IBM Corp., Armonk, NY, USA). The normality of the data distribution was assessed using appropriate tests. Normality analysis revealed that while PLCR (pre- and post-treatment), MPV (post-treatment), and LMR (pre- and post-treatment) exhibited a normal distribution ($p>0.05$), the remaining variables demonstrated a non-normal distribution ($p<0.05$). For comparisons of systemic inflammatory parameters before and after dienogest treatment, the paired Student's t-test was applied for normally distributed variables, whereas the Wilcoxon signed-rank test was used for non-normally distributed variables. Correlation analyses were conducted using two-tailed Pearson or Spearman correlation coefficients, as appropriate. Benjamini–Hochberg (FDR) correction was applied for multiple comparisons. Percentage change (Δ%) was calculated as [(after–before)/before]×100. The effect size (r) for the Wilcoxon signed-rank test was calculated using the formula $r=Z/\sqrt{N}$.

RESULTS

Variations in laboratory parameters before and after dienogest treatment are presented in **Table 1**. Regarding biochemical and hormonal assessments, a statistically significant reduction in serum CA125 levels was observed post treatment ($p=0.010$). Analysis of the hormonal profile revealed a significant elevation in FSH levels after the treatment period ($p=0.001$); however, other endocrine parameters, including LH, estradiol, prolactin, progesterone, TSH, FT3, and FT4, remained statistically stable ($p>0.05$ for all). In terms of hematological parameters, significant increases were noted in hemoglobin ($p=0.029$) and hematocrit ($p=0.002$) levels at the post-treatment evaluation. Correspondingly, red blood cell indices, specifically MCV ($p=0.012$) and MCH ($p=0.015$), demonstrated significant upward trends. Conversely, a significant decline was observed in leukocyte ($p=0.031$), and plateletcrit (PCT) ($p=0.009$) levels after therapy. Other markers, such as RDW, PDW, MPV, and P-LCR, exhibited no significant alterations ($p>0.05$). Notably, after applying the Benjamini-Hochberg False Discovery Rate (FDR) correction for multiple comparisons, platelet counts (PLT) failed to maintain statistical significance ($q>0.05$), despite an initial marginal p-value of 0.046. Analysis of inflammatory indices revealed that PLR levels significantly declined after the treatment period ($p=0.028$), However, no statistically significant differences were observed in NLR, LMR, NMR, MPVLR, SII, SIRI, or PIV values ($p>0.05$ for all).

Table 1. Comparison of laboratory parameters before and after treatment

Parameters	Before (median, IQR)	After (median, IQR)	p value
Ovarian markers			
CA125 (U/ml)	33.50 (22.00-47.50)	21.00 (15.00-36.00)	0.010*
Hormonal profile			
FSH (mIU/ml)	6.10 (4.50-8.00)	6.55 (4.90-11.10)	0.001*
LH (mIU/ml)	8.00 (5.00-12.00)	8.50 (5.60-14.80)	0.125
Estradiol (pg/ml)	90.00 (50.00-165.00)	90.00 (58.00-143.00)	0.791
Prolactin (ng/ml)	16.00 (11.00-21.00)	16.00 (11.00-21.00)	0.442
Progesterone (ng/ml)	1.10 (0.40-4.00)	1.20 (0.50-5.00)	0.156
Thyroid function			
TSH (mIU/L)	1.70 (1.10-2.40)	1.60 (1.10-2.40)	0.616
FT3 (pg/ml)	3.00 (2.80-3.30)	3.00 (2.80-3.40)	0.643
FT4 (ng/dl)	1.20 (1.10-1.30)	1.20 (1.10-1.30)	0.878
Hematological parameters			
Hemoglobin (g/dl)	12.60 (11.50-13.60)	12.90 (11.90-14.00)	0.029*
Hematocrit (%)	38.00 (35.70-41.00)	39.50 (36.80-41.90)	0.002*
Leukocyte ($x10^3/\mu L$)	7.40 (6.10-9.30)	7.10 (5.90-8.30)	0.031*
MCV (fL)	86.00 (80.00-89.00)	86.00 (82.00-90.00)	0.012*
MCH (pg)	28.50 (26.30-30.00)	28.80 (26.60-30.40)	0.015*
Inflammatory indices			
PLR	134.00 (104.00-172.00)	125.00 (104.00-152.00)	0.028*
SII	602.00 (413.00-846.00)	572.00 (421.00-817.00)	0.111
SIRI	0.88 (0.50-1.30)	0.90 (0.50-1.40)	0.646
PIV	212.00 (126.00-393.00)	224.00 (133.00-412.00)	0.471

CA125: Cancer antigen 125, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, TSH: Thyroid stimulating hormone, RDW: Red cell distribution width, PDW: Platelet distribution width, MPV: Mean platelet volume, PCT: Plateletcrit, PLCR: Platelet large cell ratio, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, NLR: Neutrophil-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte, ratio, PLR: Platelet-to-lymphocyte ratio, NMR: Neutrophil-to-monocyte ratio, MPVLR: MPV-to-lymphocyte ratio, SII: Systemic Immune-inflammation Index, SIRI: Systemic Inflammation Response Index, PIV: Pan-immune-inflammation value. After applying the Benjamini-Hochberg (FDR) correction for multiple comparisons, the difference in platelet (PLT) levels did not reach statistical significance (adjusted p=0.052)

Percentage change and effect size of laboratory parameters following dienogest treatment are presented in **Table 2**. After treatment, CA125 levels decreased by 15.1%, whereas FSH levels increased markedly by 31.0%. Hemoglobin and hematocrit increased by 2.6% and 2.5%, respectively, accompanied by modest increases in MCV (+1.0%) and MCH (+1.2%). A downward trend in systemic inflammation was also observed, reflected by a 7.5% reduction in PLR and a 5.1% decrease in leukocyte counts (**Table 2**). Correlation analysis between systemic inflammatory markers and hematological parameters is presented in **Table 3**.

Table 2. Percentage change and effect size of laboratory parameters following dienogest treatment

Parameter	Before	After	Δ% change	Effect size (r)
CA125	42.49	36.06	−15.1% ↓	0.21
FSH	8.75	11.46	+31.0% ↑	0.27
Hematocrit	38.26	39.23	+2.5% ↑	0.21
Hemoglobin	12.56	12.89	+2.6% ↑	0.21
Leukocyte	7.78	7.38	−5.1% ↓	0.18
Platelet	287.81	282.84	−1.7% ↓	0.16
PCT	0.30	0.28	−6.7% ↓	0.18
MCV	84.72	85.56	+1.0% ↑	0.21
MCH	27.93	28.26	+1.2% ↑	0.20
PLR	145.63	134.74	−7.5% ↓	0.18

CA125: Cancer antigen 125, FSH: Follicle stimulating hormone, PCT: Plateletcrit, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, PLR: Platelet-to-lymphocyte ratio

DISCUSSION

In the present study, dienogest therapy, a selective progestin, was associated with reductions in CA125 levels, a well-recognized marker of endometriosis activity, along with decreases in systemic inflammatory parameters including PLR and PCT. Concurrently, a significant increase in FSH

Table 3. Correlation analysis between systemic inflammatory markers and hematological parameters

	CA125	FSH	Hb	HCT	WBC	PLT	PCT	MCV	MCH	PLR
CA125	1.00	-0.342 (0.042)*	-0.014 (0.891)	-0.277 (0.006)**	0.042 (0.680)	0.041 (0.683)	0.087 (0.487)	-0.123 (0.228)	-0.228 (0.028)*	0.249 (0.013)*
FSH	-0.342 (0.042)*	1.00	-0.059 (0.581)	-0.093 (0.382)	-0.066 (0.538)	-0.010 (0.930)	-0.135 (0.279)	-0.116 (0.276)	-0.093 (0.382)	0.060 (0.582)
HB	-0.014 (0.891)	-0.059 (0.581)	1.00	0.933 (<0.001)**	-0.071 (0.404)	-0.116 (0.173)	-0.155 (0.069)	0.308 (<0.001)**	0.499 (<0.001)**	-0.144 (0.090)
HCT	-0.277 (0.006)**	-0.093 (0.382)	0.933 (<0.001)**	1.00	-0.054 (0.529)	-0.096 (0.258)	-0.136 (0.108)	0.306 (<0.001)**	0.518 (<0.001)**	-0.119 (0.161)
WBC	0.042 (0.680)	-0.066 (0.538)	-0.071 (0.404)	-0.054 (0.529)	1.00	0.220 (0.009)**	0.207 (0.014)*	-0.083 (0.325)	-0.200 (0.018)*	-0.072 (0.399)
PLT	0.041 (0.683)	-0.010 (0.930)	-0.116 (0.173)	-0.096 (0.258)	0.220 (0.009)**	1.00	0.877 (<0.001)**	-0.073 (0.390)	-0.156 (0.066)	0.488 (<0.001)**
PCT	0.087 (0.487)	-0.135 (0.279)	-0.155 (0.069)	-0.136 (0.108)	0.207 (0.014)*	0.877 (<0.001)**	1.00	-0.019 (0.823)	-0.114 (0.181)	0.444 (<0.001)**
MCV	-0.123 (0.228)	-0.116 (0.276)	0.308 (<0.001)**	0.306 (<0.001)**	-0.083 (0.325)	-0.073 (0.390)	-0.019 (0.823)	1.00	0.824 (<0.001)**	-0.005 (0.955)
MCH	-0.228 (0.028)*	-0.093 (0.382)	0.499 (<0.001)**	0.518 (<0.001)**	-0.200 (0.018)*	-0.156 (0.066)	-0.114 (0.181)	0.824 (<0.001)**	1.00	-0.075 (0.380)
PLR	0.249 (0.013)*	0.060 (0.582)	-0.144 (0.090)	-0.119 (0.161)	-0.072 (0.399)	0.488 (<0.001)**	0.444 (<0.001)**	-0.005 (0.955)	-0.075 (0.380)	1.00

*Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed). FSH: Follicle-stimulating hormone, PCT: Procalcitonin, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, PLR: Platelet-to-lymphocyte ratio. Following the Benjamini-Hochberg (FDR) correction for multiple comparisons, certain correlations that initially appeared significant did not maintain statistical significance (q>0.05), including CA125 and FSH (p=0.042→q=0.118), CA125 and MCH (p=0.028→q=0.084), and Leukocyte and MCH (p=0.018→q=0.057).

levels was observed, which may suggest that the pituitary axis was not entirely suppressed. Furthermore, the noted improvements in hematological parameters could potentially be attributed to a reduction in menstrual blood loss associated with the therapy. Endometriosis is widely recognized as a systemic inflammatory condition in the literature. The present findings may suggest a suppressive effect of dienogest on this inflammatory milieu. Significant reductions in leukocyte was observed, accompanied by a notable decrease in PLR, a well-established marker of systemic inflammation. Furthermore, the observed reduction in PCT levels, a marker of platelet activation, provides additional evidence for the attenuation of systemic inflammatory activity.

In line with our findings, a case control study demonstrated that systemic inflammatory markers, including NLR and PLR, were significantly elevated in patients with endometriosis compared with healthy controls. However, in contrast to our results, SII, SIRI, and PIV indices were also reported to be elevated in that study.[11] Moreover, a large-scale study involving over 10,000 patients identified a positive correlation between NLR and PLR, further supporting their utility as biomarkers of systemic inflammation in ovarian endometriosis.[12] Similarly, elevated PCT levels have been reported in patients with endometriosis.[13]

To the best of our knowledge, this is the first study to evaluate systemic inflammatory indices before and after dienogest therapy, marking a novel contribution to the existing literature. In this context, a study investigating RNA expression profiles in endometriotic tissues from patients receiving or not receiving preoperative dienogest demonstrated that dienogest modulates leukocyte activation and inflammatory signaling pathways at the molecular level.[14] The reductions in leukocyte count and PLR observed following treatment in the present study may therefore be interpreted as clinical reflections of these molecular regulatory effects. Notably, the 7.5% reduction in PLR following dienogest therapy further supports the notion that medical treatment effectively modulates the underlying inflammatory process and reduces systemic inflammatory burden.

In the present study, the 15.1% reduction in CA125 levels, a well-established biomarker associated with both epithelial ovarian cancer and endometriosis,[15] is consistent with the suppressive effects of dienogest on endometriotic lesions reported in the literature.[16] This decrease is clinically relevant, as it may reflect suppression of inflammatory activity and cellular proliferation within ectopic endometrial tissue or indicate regression of the underlying pathological process.

Another notable finding was the 31.0% increase in FSH levels. Previous evidence suggests that dienogest exerts only a moderate suppressive effect on gonadotropins. In one study, this modulatory effect enabled effective LH suppression without complete inactivation of the pituitary axis.[17] The increase in FSH observed in our study may therefore be interpreted as a dynamic response of the pituitary axis to partial suppression or as a rebound effect[18] However, no statistically significant differences were observed in LH, estradiol, or progesterone levels ($p>0.05$). While several parameters reached statistical significance ($p<0.05$), the observed effect sizes were generally small ($r<0.3$), suggesting that the immediate clinical magnitude of these changes may be limited. However, in the context of a chronic inflammatory disease like endometriosis, these alterations such as the 2.6% increase in hemoglobin and the 15.1% reduction in CA125 should be interpreted as positive biological trends rather than transformative clinical shifts.

These findings indicate that dienogest does not fully suppress the hypothalamic–pituitary–gonadal axis but rather maintains a therapeutic window at the target tissue level. By maintaining estrogen levels within a specific therapeutic window, dienogest appears to exert a protective effect on bone mineral density.[19] Supporting this observation, a case study reported that progestin therapy combined with low-dose estrogen in symptomatic patients unresponsive to conventional progestin and GnRH analog treatments resulted in complete resolution of clinical symptoms and an increase in bone mineral density over a two-year follow-up period.[20]

One of the most striking findings of the present study is the improvement observed in the hematological profile of the patients. The significant increases in hemoglobin, hematocrit, MCV, and MCH following treatment suggest a clinical consequence potentially related to dienogest-induced amenorrhea. In endometriosis, which is characterized by chronic pelvic pain and menstrual bleeding,[3] the prevention of blood loss reduces the risk of iron deficiency anemia, contributes to the preservation of iron stores, and improves overall patient condition. These findings may suggest that the therapeutic impact of dienogest could extend beyond the suppression of endometriotic lesions, potentially contributing to improvements in the patients' overall anemia profile. The observed increases in hematological parameters, particularly hemoglobin and hematocrit, appear to indicate that the intervention is unlikely to induce significant adverse effects such as bone marrow suppression; instead, it might support a more favorable general health status in this patient population. In contrast, no statistically significant differences were observed in more complex inflammatory indices, including NLR, SII, and SIRI. Consistent with previous studies, these findings suggest that the anti inflammatory effects of dienogest are primarily mediated through modulation of platelet and leukocyte homeostasis,[11,14] without markedly altering the neutrophil lymphocyte balance.

In the present study, the positive correlation identified between CA125 levels and the platelet to lymphocyte ratio PLR supports the hypothesis that endometriosis is not solely a localized pelvic disorder but also represents a systemic inflammatory condition.[1] In line with this finding, previous studies have reported that both PLR and CA125 levels are positively correlated with the severity of pelvic adhesions and that the combined use of these two parameters demonstrates high diagnostic specificity.[21] This positive association between CA125 and PLR suggests that the inflammatory burden of the disease can be monitored concurrently through both biochemical and hematological parameters.

The inverse relationship between CA125 and hematocrit observed in our study is further supported by recent longitudinal data demonstrating that women with endometriosis carry a significantly higher risk of iron deficiency, while Kawamata et al.[23] highlighted that anemia-related biomarkers are closely

linked to the clinical characteristics of the disease. In this context, the statistically significant increase in hemoglobin and hematocrit following dienogest treatment, likely mediated by a reduction in menstrual blood loss and mitigation of chronic inflammation, represents a clinically meaningful improvement in the patients' hematological health. This finding aligns with the therapeutic goals outlined in recent literature.[22,23] The significant positive correlation observed between CA125 and PLR is consistent with the findings of Sabarudin et al.,[24] reinforcing the biological plausibility that CA125 levels parallel systemic inflammatory indices in gynecological pathologies and that dienogest treatment effectively modulates both localized disease activity and this systemic inflammatory environment. In the present study, hematological parameters exhibited internal consistency. The positive correlation observed between leukocyte count and platelet and PCT levels further supports the interaction among hematological cell lineages in the context of subclinical inflammation reported in patients with endometriosis.[11]

Limitations

The primary limitation of this study is its retrospective nature, which prevents the establishment of a direct causal relationship. Furthermore, while the current sample size provides significant data, further large-scale, multicenter studies are warranted to enhance the generalizability of the findings.

CONCLUSION

Dienogest therapy was associated with a reduction in CA125 levels and certain systemic inflammatory markers, alongside improvements in hematological parameters. These findings suggest that dienogest may modulate specific pathways of systemic inflammation without achieving complete suppression of the hypothalamic–pituitary–gonadal axis.

ETHICAL DECLARATIONS

Ethics Committee Approval

All necessary ethical approvals for this retrospective study were obtained from the Ethics Committee for Non-interventional Researches at Kırıkkale University (Date: 16.10.2024, Decision No: 2024.10.01).

Informed Consent

As this was a retrospective study, formal written informed consent was not required and was therefore not obtained.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

Concept: FBA, NS; Design: FBA, NS; Control: FBA, NS; Data Collection and/or Processing: FBA; Analysis and/or Interpretation: FBA, NS; Literature Review: FBA, NS; Writing the Article: FBA, NS; Critical Review: FBA, NS.

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Investigation of the prevalence of polycystic ovary syndrome and its association with dietary habits and physical activity self-efficacy levels among university students

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ABSTRACT

Aims: This study aimed to determine the frequency of polycystic ovary syndrome (PCOS) among university students and to examine the associations of PCOS status with dietary habits and levels of physical activity self-efficacy.

Methods: This descriptive study was conducted between February and November 2025 among 524 students enrolled in the faculty of health sciences at a state university in southwestern Turkiye. Data were collected using a Descriptive Information Form, the Sustainable and Healthy Eating Behaviors Scale (SHE) and the Women's Physical Activity Self-Worth Inventory (WPASWI). PCOS status was assessed through self-report.

Results: The mean age of the participants was 20.8±2.24 years (min: 17; max: 30), and 14.9% self-reported PCOS. The mean total score of the SHE was 3.71±1.04 and the WPASWI was 108.21±18.03. No statistically significant differences were found between students with and without self-reported PCOS in terms of dietary habits or physical activity self-efficacy scores (p>0.05).

Conclusion: The self-reported prevalence of PCOS among university students was approximately 15%. Healthy dietary habits and physical activity self-efficacy were at a moderate level. No significant differences were found between students with and without self-reported PCOS in these variables. Physical activity self-efficacy was stronger in the cognitive and emotional dimensions than in the social dimension.

Keywords: Polycystic ovary syndrome, dietary habits, physical activity, self-efficacy, university students

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders among women of reproductive age, affecting approximately 10-18% depending on the diagnostic criteria and the population studied.[1,2] According to the widely used Rotterdam criteria, PCOS is diagnosed when at least two of the following are present: oligo/anovulation, clinical or biochemical hyperandrogenism, and polycystic ovary morphology. This heterogeneity indicates that PCOS is not merely a gynecological condition but a multifaceted syndrome with metabolic and psychosocial dimensions.[3,4]

In addition to infertility and pregnancy complications, cardiometabolic disorders such as insulin resistance, dyslipidemia, visceral adiposity, and metabolic syndrome are more common in women with PCOS, increasing the risk of type 2 diabetes and cardiovascular disease. Psychosocial problems, including anxiety, depression, and negative body image, have also been reported to be more prevalent in this population.[5,6] These findings demonstrate that PCOS affects quality of life across multiple dimensions.

Insulin resistance and hyperinsulinemia are key pathophysiological mechanisms of PCOS and contribute to increased hyperandrogenism.[7] Overweight and obesity may exacerbate this process. Therefore, lifestyle factors are considered central to PCOS management. The International Evidence-Based Guideline for the Assessment and Management of PCOS recommends healthy eating habits and regular physical activity as primary early interventions.[2]

Current literature suggests that fiber-rich and low–glycemic index dietary patterns may improve insulin sensitivity and metabolic parameters.[11,12] Regular physical activity has also been shown to improve body composition, insulin sensitivity, and cardiometabolic risk factors.[13,14] However, evidence regarding whether physical activity levels differ between women with and without PCOS remains inconsistent.[3]

These findings highlight the importance of evaluating lifestyle-related factors in relation to PCOS, particularly in young women. Examining dietary habits and physical activity

self-efficacy in university students may contribute to a better understanding of early lifestyle patterns associated with self-reported PCOS. Therefore, this study aimed to determine the frequency of self-reported PCOS among university students and to examine its association with dietary habits and physical activity self-efficacy.

METHODS

Ethics

The necessary permissions for this study were first obtained from the relevant university institution. This study was approved by the Ethics Committee of the Health Sciences at Muğla Sıtkı Koçman University (Date: 28.03.2025, Decision No: 43). Voluntary participation was secured from all study participants through informed consent forms, and the necessary permissions were obtained for the administration of the scales used. The entire process was conducted in accordance with the Declaration of Helsinki and applicable national legislation.

Study Design

This descriptive study was conducted between February and November 2025 among 524 students enrolled in the Faculty of Health Sciences at a state university in southwestern Turkiye. The sample size was calculated using the G*Power program based on a 95% confidence interval, 5% alpha level, and 80% statistical power.[15] The inclusion criteria were being a student in the Faculty of Health Sciences and voluntarily agreeing to participate in the study. Students with a psychiatric diagnosis, intellectual disability, or visual impairment were excluded from the study. PCOS status was assessed through self-report. Participants were asked the question, "Do you have PCOS?" and responded with "yes" or "no." The prevalence of PCOS was calculated as the proportion of participants who responded "yes" within the total sample. No clinical verification or medical record review was performed.

Data collection tools: Data were collected using an Individual Identification Form, an Informed Consent Form, the Sustainable and Healthy Eating Behaviors Scale (SHE), and the Women's Physical Activity Self-Worth Scale. The Individual Identification Form was developed by the researchers based on the literature and consisted of 17 questions addressing socio-demographic characteristics such as age, gender, and income status.

Sustainable and Healthy Eating Behaviors (SHE): This scale was developed by Zakowska-Biemans et al.[17] and was certified by Köksal et al.[16] for its reliability and validity in Turkish. Scale; It consists of a total of eight sub-dimensions and thirty-two items: healthy and balanced nutrition, quality labels (local and organic), meat reduction, local food, low fat, avoiding food waste, animal welfare and seasonal foods. It is a 7-point Likert type from the participants as 'never', 'very rarely', 'rarely', 'sometimes', 'often', 'very often' or 'always'. 'Never' is rated at 1 point and 'always' at 7 points. Sub-dimension scores are calculated by averaging the points (between 1 and 7 points) given to the items in that sub-dimension. In the calculation of the total scale score, it is calculated by taking the average of the scores given to all sub-dimensions. The Cronbach's α coefficient of the scale was found to be 0.91. In our study, the Cronbach's α coefficient was calculated as 0.96.

Women's Physical Activity Self-Worth Inventory (WPASWI): This scale is a 37-item multidimensional scale developed by Huberty et al.[31] in 2013 and validated in Turkish by Yurtçiçek and Kömürcü[18] in 2019. The CFAS is a 37-item Likert-type scale that evaluates the non-physical aspects of self-worth associated with physical activity in women. There are three sub-dimensions in the scale: knowledge self-worth, emotional self-worth, social self-worth. The total score from the scale varies between 37-148. As the score increases, the sense of self-worth increases. The Cronbach's α coefficient of the scale was found to be 0.91. In our study, the Cronbach's α coefficient was calculated as 0.96.

Data Collection Process

The research data were collected from the students included in the sample between February and July 2025, after obtaining Ethics Committee Approval and necessary permissions. The purpose of the research was explained to the participants, and they were asked to sign an "Informed Consent Form" stating that participation in the research was completely voluntary and that they could withdraw from the research at any time. Participants were also asked to fill out a Descriptive Information Form, the SHE, and the Women's Physical Activity Self-Worth Scale. In line with the appointments made in advance from the faculty and department administrations for the collection of scales and individual identification forms, the selected students were applied under observation for approximately one class hour. The application of the data collection tools took approximately 20-25 minutes for each participant and the students were allowed to fill them out individually.

Statistical Analysis

The research data were evaluated using the SPSS 30 program. The sociodemographic characteristics of the participants were determined by descriptive analyses; number, percentage, mean and standard deviation values were calculated. The normal distribution of the data was checked with the Shapiro-Wilk test. In the analysis of the data, Student's t-test was applied for independent two-group comparisons, and one-way analysis of variance (One-way ANOVA) was applied for three-way group comparisons. The differences between the scale total scores and the independent variables were examined with these methods; The statistical significance level of the results obtained was accepted as $p<0.05$.

RESULTS

The mean age of the participants was 20.8±2.24 years (min: 17; max: 30). Most participants were single and studying in the nursing department (**Table 1**). Overall, 14.9% of the students reported having PCOS.

The mean total score of the SHE was 3.71±1.04. Among the subdimensions, the highest mean score was observed in the animal welfare subdimension, whereas the lowest mean score was found in the healthy and balanced nutrition subdimension (**Table 2**). The mean total score of the WPASWI was 108.21±18.03, with the highest mean score observed in the knowledge subdimension (**Table 2**).

No statistically significant difference was found between students with and without self-reported PCOS in terms of physical activity self-efficacy scores ($t(522)=0,197$, $p=0.844$, Cohen's $d=0.024$). Similarly, no significant difference was

Table 1. Distribution of women's mean scores from the Women's Physical Activity Self-Worth Inventory and the Sustainable and Healthy Eating Behaviors Scale according to their sociodemographic characteristics (n=524)

			SHE average		WPASWI average	
Variables	**n**	**%**	**$\bar{X}$±SD**		**$\bar{X}$±SD**	
Age						
17-21	372	71.0	3.76±1.05	t=.522	118±33.1	t=.618
22-30	152	29.0	3.69±1.04	p=.514	120±33.7	p=.537
Department studied						
Nursing	253	48.3	3.51±1.03		108±19.2	
Nutrition and dietetics	98	18.7	4.13±0.98	f=7.66	110±17.5	f=2.15
Physical therapy and rehabilitation	85	16.2	3.90±0.99	p=0.001	111±16.6	p=.078
Health management	26	5.0	3.69±1.17		107±18.8	
Language and speech therapy	62	11.8	3.60±0.93		104±15.0	
Class						
1.	182	34.7	3.69±1.06		107±18.5	
2.	137	26.1	3.71±1.03	f= .600	109±15.5	f= 0.298
3.	133	25.4	3.66±1.04	p= .615	109±19.4	p= .827
4.	72	13.8	3.85±0.98		107±18.9	
Long-term residence area						
Western region	352	67.2	3.87±1.01		108±16.9	
Central region	54	10.3	3.69±1.00	f=11.21	106±21.2	f=.444
Eastern region	88	16.8	3.40±1.02	p=0.001	107±19.9	p=.722
Northern region	30	5.7	3.69±1.00		105±18.8	
Living arrangements						
Alone	37	7.1	4.13±0.94		109±16.8	
Family	139	26.5	3.78±0.99	f=5.41	109±16.5	f=1.18
Dormitory	313	59.7	3.58±1.04	p=0.001	107±19.0	p=.322
Roommate	35	6.7	4.05±1.06		113±16.5	
Income qualification status						
High	196	37.4	3.79±1.02	f=1.62	108±16.6	f=0.531
Medium	134	25.6	3.58±1.10	p=.197	107±22.3	p=.588
Low	194	37.0	3.71±1.00		109±16.0	
Body-mass index						
Normal weight	436	83.2	3.72±1.07	f=0.581	96±13.8	f=0.889
Fat	66	12.6	3.57±1.04	p=.560	93±14.2	p=.412
Obese	22	4.2	3.76±1.15		97±11.3	
Status of regular physical exercise						
Regular	45	8.6	4.28±1.01	f=16.254	90±11.6	f=15.863
Sometimes	351	67.0	3.77±0.99	p=0.001	98±11.7	p=0.001
None	128	24.4	3.32±1.17		91±17.5	
Smoking status						
Yes	123	23.5	3.46±1.05	t=-2.866	94±15.5	t=-1.255
No	401	76.5	3.78±1.06	p=0.004	96±13.1	p=.252
Alcohol use status						
Yes	163	31.1	3.44±1.01	t=-3.755	94±13.8	t=-1.636
No	361	68.9	3.82±1.07	p=0.001	96±13.6	p=.103
A chronic disease condition						
Yes	52	9.9	4.04±1.03	t=2.413	94±13.0	t=-0.682
No	472	90.1	3.66±1.06	p=.016	96±13.8	p=.495

$\bar{X}$: Arithmetic mean, SD: Standard deviation, SHE: Sustainable and Healthy Eating Behaviors Scale, WPASWI: Women's Physical Activity Self-Worth Inventory

observed between the groups in terms of dietary behavior scores (t(522)=-0.185, p=0.854, Cohen's d=-0.023).

When the scale scores were examined according to sociodemographic characteristics, SHE scores differed significantly by department of study, region of long-term residence, living arrangement, regular physical activity, smoking status, alcohol use, and presence of chronic disease. However, no significant differences were found according to age, grade level, income adequacy, or body-mass index. WPASWI scores differed significantly only according to regular physical exercise status, while no significant differences were observed for other sociodemographic variables (**Table 1**).

DISCUSSION

This study examined the frequency of self-reported PCOS and its association with dietary habits and physical activity self-efficacy among university students. PCOS is a common endocrine disorder among women of reproductive age, and its prevalence varies depending on the diagnostic criteria used. In the present study, 14.9% of the students reported having PCOS. Although this rate is higher than the prevalence reported in Turkiye (8.5%), it is comparable to the global prevalence reported using the Rotterdam criteria (12.1%) and the prevalence reported for the Eastern Mediterranean region (15.1%).[19,29] The relatively higher prevalence observed in this study may be related to the characteristics of the study sample.

Table 2. Score Distribution of the Sustainable and Healthy Eating Behaviors Scale and the Women's Physical Activity Self-Worth Inventory (n=524)

Scale/subscale	$\bar{X}$±SD	Min-max
Sustainable and Healthy Eating Behaviors		
Healthy and balanced diet	3.46±1.07	1-7
Certification and quality labels	3.55±1.13	1-7
Meat reduction	3.75±1.36	1-7
Selection of local food	4.21±1.30	1-7
Choice of low-fat food products	3.77±1.29	1-7
Seasonal food and avoidance of food waste	3.59±1.19	1-7
Animal welfare	4.26±1.43	1-7
Total of scale	3.71±1.04	1-7
Women's Physical Activity SelfWorth Inventory		
Knowledge subscale	48.40±8.74	16-64
Emotional subscale	45.26±14.28	13-88
Social subscale	19.95±5.22	7-32
Total of scale	108.21±18.03	37-148

$\bar{X}$: Arithmetic mean, SD: Standard deviation, Min: Minimum, Max: Maximum

The findings showed that participants' sustainable and healthy eating behaviors were at a moderate level. Previous studies conducted with university students have similarly reported moderate levels of sustainable and healthy dietary behaviors, although the highest and lowest scoring subdimensions varied across studies.[16,20,21,30] These differences may be related to variations in sample characteristics, sociodemographic structures, and cultural dietary patterns.

In the present study, sustainable and healthy eating behavior scores increased with the frequency of regular physical exercise. Similarly, Küçükcankurtaran[22] reported that dietary behavior scores increased as physical activity levels increased among university students. Higher SHE scores were also observed among students studying in the department of nutrition and dietetics and among those who did not smoke or consume alcohol. These findings are consistent with previous research reporting a relationship between smoking status and dietary behaviors.[30] The higher dietary behavior scores observed among individuals with chronic diseases may be related to increased awareness of healthy eating due to more frequent contact with healthcare professionals and nutrition counseling.[23] In this study, however, no significant differences in SHE scores were observed according to age, grade level, income adequacy, or body-mass index. This finding is consistent with previous studies reporting no significant associations between these sociodemographic variables and healthy dietary behaviors.[24,30]

In terms of physical activity self-efficacy, the mean WPASWI total score was 108.21±18.03, with the highest mean score observed in the knowledge subdimension. A similar result was reported in a study conducted with nursing students, where the mean WPASWI score was 108.37±14.49 and the knowledge subdimension had the highest score.[26] In the present study, WPASWI scores differed significantly only according to regular physical exercise status, while other sociodemographic variables were not associated with significant differences. Previous studies have also reported that higher physical activity levels are associated with improved self-perception outcomes.[27,28]

Importantly, no statistically significant differences were found between students with and without self-reported PCOS in terms of dietary habits or physical activity self-efficacy scores. These findings suggest that, within this university sample, self-reported PCOS status was not associated with differences in these lifestyle-related variables. However, given the multifactorial nature of PCOS and the cross-sectional design of this study, further research with clinically verified diagnoses and longitudinal designs is needed to better understand these relationships.

Limitations

This study was carried out with a limited number of participants and within a certain time frame. Furthermore, since the research was conducted only on a specific sample, the generalizability of the results is limited. The fact that PCOS status was assessed solely through self-report my have led to misclassification and recall bias.

CONCLUSION

This study shows that the prevalence of self-reported PCOS among university students is approximately 15%, and that dietary habits and physical activity self-efficacy levels are generally moderate. Among the SHE, the highest scores were observed in animal welfare and local food preferences, whereas relatively lower scores were recorded for healthy and balanced nutrition and reading quality labels. These results indicate a limited consistency between knowledge and actual daily practices in sustainable healthy eating behaviours. Participants' cognitive and emotional perceptions of physical activity are stronger than the social dimension. Overall, although there is a positive awareness base among young women, multidimensional interventions are needed to support the translation of this awareness into sustained behavior.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Ethics Committee of the Health Sciences at Muğla Sıtkı Koçman University (Date: 28.03.2025, Decision No: 43).

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights—including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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Author Contributions

Concept: YK, SD; Design: YK, SD; Control: YK; Resources: YK; Materials: YK; Data Collection and/or Processing: YK; Analysis and/or Interpretation: YG, SD, YK; Literature Review: YG, SD; Article Writing: YG, SD; Critical Review: YG, SD, EA.

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The association between intolerance of uncertainty and depression, anxiety, and stress among women with gynecological cancer in Turkiye: a cross-sectional study

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ABSTRACT

Aims: This study aimed to examine the association between intolerance of uncertainty (IU) and psychological distress (depression, anxiety, and stress) in women with gynecological cancer in Turkiye.

Methods: This cross-sectional study was conducted between February and July 2024, and included 139 women diagnosed with gynecological cancer at a university hospital in Ankara, Turkiye. Data were collected using a personal information form, the Intolerance of Uncertainty Scale-12, and the Depression, Anxiety, and Stress Scale-21. Statistical analyses included independent-samples t-tests, analysis of variance, Pearson correlations, and hierarchical linear regression.

Results: The mean depression, anxiety, and stress scores were 6.78±5.47, 5.73±4.12, and 7.91±4.86, respectively. IU was positively correlated with depression (r=0.437, p=0.001), anxiety (r=0.394, p=0.001), and stress (r=0.516, p=0.001). Regression analyses showed that IU was independently associated with depression (β=0.389, p=0.001), anxiety (β=0.377, p=0.001), and stress (β=0.485, p=0.001) after controlling for selected sociodemographic and clinical variables.

Conclusion: Higher IU was significantly associated with greater psychological distress in women with gynecological cancer. These findings suggest that psychosocial care may benefit from greater attention paid to uncertainty-related distress.

Keywords: Intolerance of uncertainty, gynecological cancer, depression, anxiety, stress

INTRODUCTION

Gynecological cancers, including cervical, ovarian, endometrial, vaginal, and vulvar malignancies, constitute a major global health burden due to their high incidence, complex treatments, and substantial psychosocial impact.[1,2] According to GLOBOCAN 2022, they account for approximately 1.47 million new cases and 680,000 deaths worldwide.[1,3] In Turkiye, uterine corpus, ovarian, and cervical cancers similarly remain among the most common cancers in women, contributing significantly to the national burden.[3]

Women diagnosed with gynecological cancer frequently experience substantial psychological distress, particularly depression, anxiety, and stress.[4-6] Uslu-Sahan et al.[6] reported that higher distress levels were associated with unmet spiritual care needs and poorer quality of life in Turkish women. This burden is driven by treatment side effects, illness-related uncertainty, and concerns about fertility, sexuality, and family roles.[7-9] Meta-analyses and guidelines consistently document high rates of mood and anxiety disorders in oncology populations, with nearly one-third of patients experiencing clinically significant anxiety, highlighting the need for systematic psychosocial screening and support.[4,10-12] Women with ovarian cancer appear especially vulnerable, showing higher depression and anxiety levels than the general population.[12,13]

A growing body of evidence identifies intolerance of uncertainty (IU), defined as the tendency to perceive ambiguous or unpredictable situations as threatening, as a key cognitive mechanism underlying psychological distress.[14] IU increases threat appraisal, promotes persistent worry, and impairs emotion regulation.[15,16] In oncology populations, higher IU has been consistently associated with greater depression and anxiety, fear of disease progression, and poorer cognitive functioning, and it has been shown to mediate the effects of illness-related uncertainty on psychological outcomes, supporting its role

as a transdiagnostic vulnerability factor.[15,17,18] However, most of the available evidence has been derived from broader oncology populations, and the association between IU and psychological distress in women with gynecological cancer remains less clearly characterized.[15,16,18]

In Turkiye, women with gynecological cancer have been reported to experience substantial psychological distress and supportive care needs, which may contribute to an overall psychosocial burden.[6,19,20] Additionally, sexuality and reproductive health may be experienced as sensitive or stigmatized topics in the Turkish context, potentially limiting open communication and coping resources for some women.[21] Therefore, examining the association between IU and depression, anxiety, and stress in Turkish women with gynecological cancer may provide context-specific evidence to inform psychosocial assessment and supportive care. Accordingly, this study aimed to examine the association between IU and depression, anxiety, and stress among Turkish women with gynecological cancer, while accounting for selected sociodemographic and clinical characteristics. We hypothesized that higher IU would be associated with higher levels of depression, anxiety, and stress.

METHODS

Ethics

The study protocol was approved by the Researches Ethics Committee of the Faculty of Health Sciences at Hacettepe University (Date: 05.12.2023, Decision No: 2023/08-22). Following approval by the ethics committee, research authorization was obtained from the Education Planning Committee of the Gülhane Health Application and Research Center (Date: 10.01.2024, Decision No: 1). The study followed the Declaration of Helsinki and relevant guidelines and regulations. After being informed about the potential risks and benefits of the study, each participant provided written informed consent.

Study Design

This study employed a descriptive cross-sectional design, following the guidelines outlined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[22]

Participants

Participants were recruited between February and July 2024 from the gynecological oncology inpatient and outpatient chemotherapy units of a university hospital in Ankara, Turkiye. A convenience sampling approach was used. Eligible participants were women who had received a diagnosis of gynecological cancer at least two months prior, were aware of their diagnosis, and were able to read, write, and understand Turkish. Additionally, participants provided informed consent after being informed about the study objectives. Patients with a pre-existing psychiatric disorder diagnosed prior to the cancer diagnosis or with severe visual, hearing, or speech impairments that could interfere with questionnaire completion were excluded from the study.

The required sample size was calculated using G*Power 3.1.9.2, based on a multiple regression model with a small-to-medium effect size (f^2=0.10), 95% power, and a significance level of 0.05. The minimum required sample size was 132 participants.[23] During the study period, 150 women were assessed for eligibility. Of these, 11 were excluded because they had received their diagnosis within the previous two months (n=7), had insufficient Turkish literacy (n=2), or had a pre-existing psychiatric disorder (n=4). The final sample consisted of 139 women. The recruitment yield was 92.7% (139/150).

Data Collection Tools

Data were collected using standardized instruments to assess participants' sociodemographic and clinical characteristics, IU, and levels of depression, anxiety, and stress.

Personal Information Form: The researchers developed a personal information form to collect participants' sociodemographic and clinical characteristics, including age, marital status, education, employment status, income level, cancer diagnosis, cancer stage, treatment type, and time since diagnosis. Treatment type was categorized as either single or combined treatment.

Intolerance of Uncertainty Scale: The 12-item Intolerance of Uncertainty Scale (IUS-12)[14] was used to assess participants' levels of IU. The Turkish version of the scale was validated by Sarıçam et al.[24] Items are rated on a 5-point Likert scale (1="not at all characteristic of me" to 5="entirely characteristic of me"), with total scores ranging from 12 to 60. Higher scores indicate greater IU. In the present study, Cronbach's α for the IUS-12 was 0.907.

Depression, Anxiety, and Stress Scale (DASS-21): DASS-21 was employed to measure participants' levels of depression, anxiety, and stress. The Turkish version was validated by Sarıçam.[26] The scale includes three 7-item subscales for depression, anxiety, and stress, scored on a 4-point Likert scale (0="did not apply to me at all" to 3="applied to me very much or most of the time"). In the present study, raw DASS-21 subscale scores were used, and interpretation was based on the cut-off values reported for the Turkish version (depression ≥5, anxiety ≥4, stress ≥8). Cronbach's α coefficients were 0.862 for depression, 0.783 for anxiety, and 0.819 for stress in the present study.

Data Collection Procedure

Data were collected through face-to-face interviews conducted by the first author. Participants who met the inclusion criteria were fully informed about the study's purpose, significance, and potential contributions. Written informed consent was obtained from all participants prior to data collection.

Participants completed the questionnaires independently; however, the researcher was able to provide clarification, if needed. For participants with reading difficulties, the researcher read the items aloud and indicated their responses to the questionnaires. Confidentiality was strictly maintained throughout the data-collection process. Each session lasted approximately 25–30 min per participant.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics, including frequencies, percentages, means, and standard deviations, were used to summarize participants' demographic, clinical, and scale characteristics. The normality of continuous variables was assessed prior to analysis. Comparisons of DASS-21 subscale scores across demographic and clinical variables were performed using Independent-samples t-tests and one-way analysis of variance (ANOVA). Relationships

between scale scores were examined using Pearson's correlation analysis. For each DASS-21 subscale outcome (depression, anxiety, and stress), hierarchical linear regression analyses were conducted in two steps. In model 1, variables that showed a significant association with the relevant outcome in univariate analyses ($p<0.05$) were entered. In model 2, IU was added to examine its independent association with the outcome. Regression assumptions were evaluated by examining multicollinearity (variance inflation factor and tolerance values), independence of residuals (Durbin–Watson statistic), normality of residuals using histograms and normal P–P plots, and homoscedasticity using scatterplots of standardized residuals against standardized predicted values. Two-tailed tests were used, and statistical significance was set at $p<0.05$.

RESULTS

Table 1 presents the sociodemographic and clinical characteristics of the participants. The mean age of the participants was 55.18±11.42 years (range, 25–84). Most participants had completed primary education (69.1%), were married (71.2%), were not employed (76.3%), and reported a monthly income approximately equal to their expenses (53.2%). Regarding cancer type and clinical characteristics, 47.5% of participants were diagnosed with ovarian cancer, 69.1% were in the early stages (stage 1 or 2), and 66.2% received combined therapy. The mean time since diagnosis was 16.93±21.97 months (range=2-108) (**Table 1**).

Table 1. Descriptive characteristics of the participants (n=139)

Characteristics	Mean±SD/n	Min–max/%
Age (years)	55.18±11.42	25-84
Education level		
Primary education	96	69.1
High school or above	43	30.9
Marital status		
Married	99	71.2
Single	40	28.8
Employment status		
Yes	33	23.7
No	106	76.3
Income level		
Less than expenses	32	23.0
Equal to expenses	74	53.2
More than expenses	33	23.7
Cancer diagnosis		
Cervical cancer	32	23.0
Endometrial cancer	41	29.5
Ovarian cancer	66	47.5
Cancer stage		
Early (stage 1-2)	96	69.1
Advanced (stage 3-4)	43	30.9
Treatment type*		
Single	47	33.8
Combined	92	66.2
Time since diagnosis (months)	16.93±21.97	2-108

SD: Standard deviation, Min: Minimum, Max: Maximum. *Single treatment includes surgery, chemotherapy, or radiotherapy; Combined treatment includes surgery+chemotherapy, chemotherapy+radiotherapy, surgery+chemotherapy+radiotherapy, surgery+hormone therapy, or surgery+ radiotherapy

Table 2 presents the results of the univariate analyses for the DASS-21 subscales (depression, anxiety, and stress). For the depression subscale, older age (r=0.234, p=0.006), primary education (t=2.438, p=0.016), and lower income than expenses (F=3.879, p=0.023) were associated with higher depression scores. For the anxiety subscale, older age (r=0.244, p=0.004) and unemployment (t=–2.168, p=0.033) were associated with higher anxiety scores. Regarding the stress subscale, older age (r=0.195, p=0.021) and lower income than expenses (F=3.538, p=0.032) were associated with higher stress scores.

Table 3 presents the descriptive statistics of the scales and the correlations between the DASS-21 subscales and IU. The mean scores for depression, anxiety, and stress were 6.78±5.47 (range=0–21), 5.73±4.12 (range=0-18), and 7.91±4.86 (range=0-21), respectively. The mean score on the IUS-12 was 41.88±12.12 (range=16-60). Based on the cut-off values reported for the Turkish version of the DASS-21, the mean depression and anxiety scores were above the symptom cut-offs, whereas the mean stress score was close to, but slightly below, the corresponding cut-off. Positive and significant correlations were found between IU and depression (r=0.437, p=0.001), anxiety (r=0.394, p=0.001), and stress (r=0.516, p=0.001).

Table 4 presents the results of the hierarchical linear regression analyses examining the factors associated with depression, anxiety, and stress. No multicollinearity was detected, as the variance inflation factor values were below 10 and tolerance values exceeded 0.1. Durbin–Watson statistics ranged from 1.388 to 1.524, indicating independence of residuals. Visual inspection of residual histograms, normal P–P plots, and scatterplots of standardized residuals against standardized predicted values suggested no major deviation from normality or homoscedasticity. For depression, model 1 was significant (F=5.672, p=0.001), explaining 11% of the variance (adjusted R^2=0.09). Lower income was significantly associated with higher depression scores (β=0.209, p=0.011). After IU was added in model 2, the model remained significant (F=11.564, p=0.001) and explained 26% of the variance (adjusted R^2=0.23). IU was independently associated with higher depression scores (β=0.389, p=0.001), while income level remained significantly associated with depression (β=0.158, p=0.038). For anxiety, model 1 was significant (F=4.862, p=0.009), accounting for 7% of the variance (adjusted R^2=0.05). Older age was significantly associated with higher anxiety scores (β=0.218, p=0.013). In model 2, the inclusion of IU significantly improved model fit (F=11.768, p=0.001), explaining 21% of the variance (adjusted R^2=0.19). IU was independently associated with higher anxiety scores (β=0.377, p=0.001), and age remained significantly associated with anxiety (β=0.181, p=0.026). For stress, model 1 was significant (F=5.691, p=0.004), explaining 8% of the variance (adjusted R^2=0.06). Older age (β=0.181, p=0.030) and lower income (β=0.198, p=0.018) were significantly associated with higher stress scores. After adding IU, model 2 showed a marked increase in explained variance (R^2=0.31; adjusted R^2=0.29; F=19.949, p=0.001). IU was independently associated with higher stress scores (β=0.485, p=0.001).

DISCUSSION

This study examined the association between IU and depression, anxiety, and stress among women with gynecological cancer in Turkiye. Higher IU was significantly associated with greater psychological distress and remained independently associated with depression, anxiety, and

Table 2. Univariate analysis of DASS-21 subscales

Characteristic	Depression			Anxiety			Stress		
	Mean±SD	t/F/r	p	Mean±SD	t/F/r	p	Mean±SD	t/F/r	p
Age (years)	-	0.234	0.006	-	0.244	0.004	-	0.195	0.021
Education level									
Primary school	7.52±5.75	2.438	0.016	6.10±4.43	1.623	0.107	8.28±5.11	1.336	0.184
High school or above	5.12±4.43			4.88±3.22			7.09±4.20		
Marital status									
Married	6.58±5.68	-0.681	0.497	5.45±4.19	-1.227	0.222	7.80±4.99	-0.440	0.661
Single	7.28±4.96			6.40±3.90			8.20±4.57		
Employment status									
Yes	6.27±4.70	-0.605	0.546	4.61±3.04	-2.168	0.033	7.06±3.60	-1.156	0.168
No	6.93±5.70			6.08±4.36			8.18±5.18		
Income status									
Less than expenses	8.97±6.23[a]	3.879	0.023	6.97±4.84	1.985	0.141	9.78±5.38[a]	3.538	0.032
Equal to expenses	5.81±5.26[b]			5.26±3.88			7.09±4.76[b]		
More than expenses	6.82±4.61			5.58±3.76			7.94±4.13		
Diagnosis									
Cervical cancer	8.19±5.53	2.023	0.136	6.25±4.54	0.383	0.683	8.06±5.00	1.322	0.270
Endometrial cancer	7.10±5.00			5.73±4.05			8.83±5.11		
Ovarian cancer	5.89±5.63			5.47±3.99			7.27±4.61		
Cancer stage									
Early (stage 1–2)	5.45±0.56	0.114	0.909	4.09±0.42	0.055	0.956	4.93±0.50	-0.290	0.772
Advanced (stage 3–4)	5.57±0.85			4.25±0.65			4.77±0.73		
Treatment type									
Single	7.13±5.80	0.539	0.591	6.17±4.71	0.906	0.366	8.17±5.50	0.443	0.658
Combined	6.60±5.32			5.50±3.80			7.78±4.53		
Time since diagnosis (months)	-	-0.078	0.359	-	-0.019	0.825	-	0.084	0.326

DASS-21: Depression, Anxiety, and Stress Scale, SD: Standard deviation, a, b: Groups with different letters for each variable in the same column are significant. Bonferroni test t: Student's t-test, F: One-Way Analysis of Variance (ANOVA), r: Pearson correlation

Table 3. Relationship between sociodemographic characteristics, depression, anxiety stress, and intolerance of uncertainty

Scale	Mean	SD	Min–max	Intolerance of uncertainty	
				r	p
Depression	6.78	5.47	0-21	0.437	0.001
Anxiety	5.73	4.12	0-18	0.394	0.001
Stress	7.91	4.86	0-21	0.516	0.001
Intolerance of uncertainty	41.88	12.12	16-60	-	-

SD: Standard deviation, Min: Minimum, Max: Maximum, r: Pearson correlation

stress after controlling for selected sociodemographic and clinical variables. These results support the view that IU may represent an important transdiagnostic cognitive correlate of psychological distress in oncology populations. From a psychological perspective, individuals with higher IU may be more likely to perceive illness-related ambiguity, uncertainty about prognosis, and treatment-related unpredictability as threatening, thereby intensifying worry, emotional distress, and difficulties in coping.[15-18] However, because of the cross-sectional design, these findings should be interpreted as associations rather than evidence of temporal or causal relationships.

In our study, the mean depression score was above the symptom cut-off reported for the Turkish version of the DASS-21, suggesting the presence of depressive symptoms among women with gynecological cancer. In univariate analyses, older age, lower education, and lower income were associated with higher depression scores, consistent with previous research linking sociodemographic disadvantage to poorer psychological outcomes in oncology populations.[27,28] After adjusting for selected sociodemographic and clinical variables, IU remained independently associated with depression, indicating that IU may be an important cognitive vulnerability related to persistent distress in cancer survivors.[15,16,18,29] Difficulty tolerating ambiguity regarding disease progression, treatment outcomes, and future life roles may increase worry, emotional distress, and depressive affect.[15-18] In clinical practice, these results highlight the value of paying closer attention to how patients respond to uncertainty during psychosocial assessment.[30-32]

In the present study, the mean anxiety score was above the symptom cut-off reported for the Turkish version of the DASS-21, indicating the presence of anxiety symptoms in the sample. Univariate analyses showed that older age and unemployment were associated with higher anxiety scores. This pattern is consistent with previous evidence showing that anxiety is common in oncology populations and may be shaped by social and clinical stressors.[5,30] After adjustment, IU remained independently associated with anxiety, together with older age, in line with prior research suggesting that IU may function as an important cognitive vulnerability factor in cancer populations.[16,29] Greater IU may heighten attention

Table 4. Hierarchical linear regression analysis of the determinants of DASS-21 subscales

Dependent variable	Independent variables[a]	Model 1				Model 2				DW	Collinearity statistics	
		B	SE	β	p	B	SE	β	p		Tolerance	VIF
Depression	Age	0.078	0.043	0.162	0.072	0.074	0.039	0.156	0.061	1.440	0.821	1.218
	Education (1=primary)	1.616	1.053	0.137	0.127	0.896	0.977	0.076	0.361		0.808	1.237
	Income (1=income <expenses)	2.708	1.053	0.209	0.011	2.050	0.976	0.158	0.038		0.977	1.024
	Intolerance of uncertainty					0.176	0.034	0.389	0.001		0.956	1.046
	F (p)	5.672 (0.001)				11.564 (0.001)						
	R^2	0.11				0.26						
	adjR^2	0.09				0.23						
	R^2 change	-				0.15						
Anxiety	Age	0.079	0.031	0.218	0.013	0.065	0.029	0.181	0.026	1.524	0.906	1.103
	Employment (1=no)	0.853	0.836	0.088	0.309	0.926	0.773	0.096	0.233		0.914	1.094
	Intolerance of uncertainty					0.128	0.026	0.377	0.001		0.991	1.009
	F (p)	4.862 (0.009)				11.768 (0.001)						
	R^2	0.07				0.21						
	adjR^2	0.05				0.19						
	R^2 change	-				0.14						
Stress	Age	0.077	0.035	0.181	0.030	0.060	0.031	0.141	0.053	1.388	0.988	1.012
	Income (1=income <expenses)	2.281	0.950	0.198	0.018	1.581	0.833	0.137	0.060		0.979	1.021
	Intolerance of uncertainty					0.195	0.029	0.485	0.001		0.976	1.025
	F (p)	5.691 (0.004)				19.949 (0.001)						
	R^2	0.08				0.31						
	adjR^2	0.06				0.29						
	R^2 change	-				0.23						

DASS-21: Depression, Anxiety, and Stress Scale, B: Unstandardized coefficient, β: Standardized coefficient, SE: Standard error, DW: Durbin-Watson, VIF: Variance inflation factor. Predictors included in the final model were those statistically significant in univariate analyses (p<0.05). a: Only variables significant in univariate analyses were entered into the regression models.

to illness-related ambiguity and future-oriented threat, thereby amplifying anticipatory worry and anxiety during the cancer experience.[15-18] Supportive care may therefore benefit from addressing uncertainty-related cognitions and coping responses in women with elevated anxiety.

In our sample, the mean stress score was close to the symptom cutoff reported for the Turkish version of the DASS-21, suggesting a notable level of stress symptoms. In univariate analyses, older age and lower income were associated with higher stress scores, consistent with previous research reporting elevated stress and maladaptive coping among women with gynecological cancer.[28] In the adjusted model, IU showed the strongest association with stress, in line with evidence linking IU to heightened affective symptoms in oncology populations.[16] For women coping with ongoing treatment demands and uncertainty about recovery, high IU may make everyday illness-related demands feel less manageable, contributing to tension, emotional overload, and perceived stress.[15-18] This pattern underscores the importance of supportive care that addresses both uncertainty-related cognitions and socioeconomic vulnerability.

Limitations

This study has several limitations that should be considered when interpreting the findings. Owing to the cross-sectional design, the directionality and temporal ordering of the observed associations cannot be established, and causal inferences should be avoided. Data were collected from a single university hospital in Turkiye using a convenience sample, which may limit the generalizability of the findings to other settings or populations and increase the risk of selection bias. Additionally, reliance on self-report measures may introduce social desirability or recall bias. Although several clinical characteristics were included, recurrence status and metastatic disease were not available in the dataset and therefore could not be examined as potential confounders.

CONCLUSION

This study showed that higher IU was significantly associated with higher levels of depression, anxiety, and stress among women with gynecological cancer in Turkiye, even after adjusting for selected sociodemographic and clinical characteristics. These findings highlight the importance of considering uncertainty-related cognitive responses in psychosocial care for this patient group. Routine psychosocial assessment that considers IU, together with evidence-based interventions such as IU-focused cognitive-behavioral and acceptance-based approaches, may help strengthen coping with uncertainty and reduce emotional burden. Future longitudinal and multi-center studies are needed to clarify temporal relationships and further examine the role of IU in psychological adaptation among women with gynecological cancer.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study protocol was approved by the Researches Ethics Committee of the Faculty of Health Sciences at Hacettepe University (Date: 05.12.2023, Decision No: 2023/08-22). Following approval by the ethics committee, research

authorization was obtained from the Education Planning Committee of the Gülhane Health Application and Research Center (Date: 10.01.2024, Decision No: 1).

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights—including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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Author Contributions

Concept: MŞA, FUŞ, NK, TA; Design: MŞA, FUŞ, NK, TA; Control: MŞA, FUŞ, NK, TA; Resources: MŞA, FUŞ, NK, TA; Materials: MŞA, FUŞ, NK, TA; Data Collection and/or Processing: MŞA, FUŞ, NK, TA; Analysis and/or Interpretation: MŞA, FUŞ, NK, TA; Literature Review: MŞA, FUŞ, NK, TA; Article Writing: MŞA, FUŞ, NK, TA; Critical Review: MŞA, FUŞ, NK, TA.

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Review

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Urogynecological examination and simulated operations within the Integral Theory framework; a narrative review

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ABSTRACT

Pelvic floor dysfunction is commonly assessed using symptom-based classification and static anatomical examination; however, the relationship between pelvic floor anatomy and symptom generation is often complex. Within this context, the Integral Theory offers a functional and compartment-based framework that relates pelvic floor symptoms to defects in specific ligamentous and fascial supports. A central component of this approach is the concept of the simulated operation, in which temporary mechanical support is applied to a suspected anatomical defect to determine whether symptoms improve. This review summarizes the principles of urogynecological examination within the Integral Theory framework, with emphasis on the three vaginal zones, their associated symptom patterns, and the clinical role of simulated operations in the anterior, middle, and posterior compartments. Particular attention is given to the practical value of these maneuvers as dynamic bedside tests that help link symptoms to compartment-specific support failure. The review also discusses their relevance in contemporary urogynecological practice, especially in women with complex, overlapping, or disproportionate symptoms, as well as their limitations, including examiner dependence and subjective symptom interpretation. Simulated operations should not be viewed as stand-alone diagnostic tools, but as clinically useful adjuncts that complement history, examination, imaging, and other investigations. Within a structured diagnostic pathway, they may refine clinical reasoning, support compartment-specific management, and strengthen the functional correlation between anatomy and symptom expression.

Keywords: Integral Theory, urogynecological examination, simulated operation, stress urinary incontinence, posterior fornix syndrome

INTRODUCTION

Pelvic floor dysfunction is traditionally approached through symptom-based classification and static anatomical assessment. However, many urogynecological symptoms overlap, and the relationship between anatomy and symptom generation is not always straightforward.[1] Within this context, the Integral Theory[2] proposed a compartment-based and functional interpretation of pelvic floor disorders, emphasizing the role of connective tissue laxity, ligamentous support, and dynamic muscle action in maintaining normal pelvic organ function.[3] In this model, dysfunction is not viewed solely as an organ-specific disorder, but as the consequence of disturbed interactions between pelvic organs, their supporting ligaments and fascia, and the reflex muscle forces acting upon them.

A central concept of the Integral Theory is that connective tissue damage may be assessed within three vaginal zones (**Figure 1**) which form the basis of its diagnostic system, surgical anatomy, and treatment strategy. This zonal approach was developed to correlate characteristic symptom complexes with defects in specific anatomical supports and to guide targeted reconstructive procedures. Rather than relying only on static findings, the theory frames pelvic floor assessment as a dynamic clinical process in which structure and function must be interpreted together.

An important diagnostic extension of this framework is the concept of the simulated operation. In the Integral Theory system, simulated operations are used to verify the suspected zone of anatomical damage by temporarily restoring support and observing whether symptoms improve. Petros[3] describes this method as a valuable part of the diagnostic pathway because it allows preoperative direct testing of symptom causation. In this sense, simulated operations are not merely examination maneuvers; they are functional bedside tests designed to connect anatomy with symptom expression.

The aim of this review is to summarize the principles of urogynecological examination within the Integral Theory framework, with particular emphasis on the anatomical basis of the three vaginal zones, the rationale and technique of simulated operations, their clinical interpretation, and their

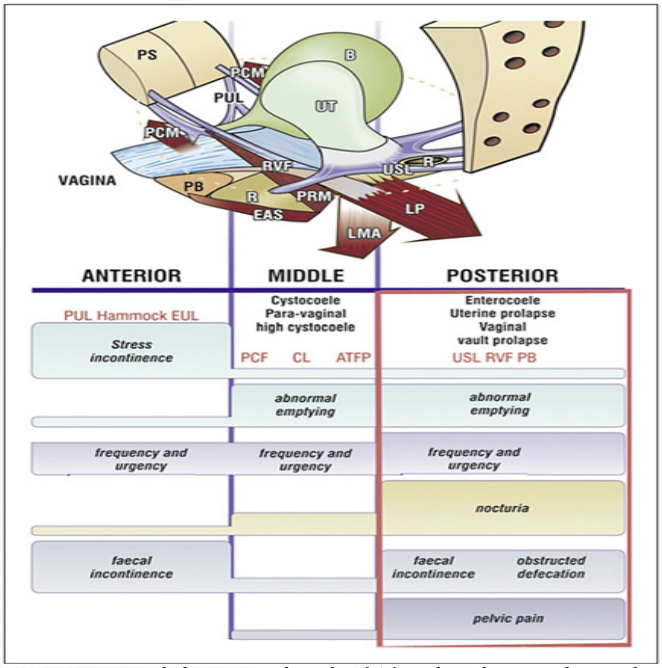

Figure 1. Pictorial diagnostic algorithm.[3] This algorithm correlates pelvic floor symptoms with the ligaments most likely to be damaged. Each symptom is marked in the relevant box, allowing the associated ligament defect and prolapse pattern to be identified.

PUL: Pubourethral ligament, suburethral hammock. EUL: External urethral ligament, CL: Cardinal ligament, PCF: Pubocervical fascia, ATFP: Arcus tendineus fascia pelvis, RVF: Rectovaginal fascia, USL: Uterosacral ligament

potential value in linking pelvic floor symptoms to specific compartmental defects.

THE THREE VAGINAL ZONES AND THEIR SYMPTOM ASSOCIATIONS

Within the Integral Theory framework, the connective tissue structures responsible for pelvic organ support and symptom generation are organized into three functional vaginal zones: anterior, middle, and posterior. This zonal classification forms the basis of the pictorial diagnostic algorithm, in which symptoms are used to predict the most likely site of connective tissue damage and the associated prolapse pattern. Rather than viewing prolapse and pelvic floor symptoms as separate entities, this approach links specific symptom complexes to defects in particular ligamentous and fascial supports.

The anterior zone extends from the external urethral meatus to the bladder neck and is mainly associated with the pubourethral ligament and suburethral hammock. Defects in this zone are classically linked to stress urinary incontinence, reflecting impaired urethral support during increases in intra-abdominal pressure.[3]

The middle zone extends from the bladder neck to the anterior cervical ring and includes structures such as the pubocervical fascia, cardinal ligament, and arcus tendineus fascia pelvis. Damage in this compartment may contribute to cystocele-related dysfunction and may also be associated with storage symptoms, depending on the pattern and extent of support failure.[3]

The posterior zone extends from the posterior cervical ring to the perineal body and is closely related to the uterosacral ligaments and rectovaginal fascia.

An important strength of this zonal model is that it provides a practical bridge between anatomy and symptoms. Although overlap between compartments is common, the algorithm offers a structured way to interpret symptom patterns during urogynecological examination and may help guide both diagnostic maneuvers and compartment-specific reconstructive strategies.

Within the Integral Theory framework,[2] simulated operations are used as dynamic clinical maneuvers to verify the suspected site of connective tissue damage. Rather than relying solely on static examination findings, they aim to temporarily restore support to a suspected anatomical defect and observe whether symptoms improve.

The rationale for these maneuvers lies in the dynamic nature of symptom formation. According to the Integral Theory, symptoms do not arise simply from visible prolapse, but from altered interactions among connective tissue, muscles, and sensory nerves.[4] As a result, even minor anatomical defects may produce major symptoms, and the full extent of structural weakness may not always be obvious on routine examination.

Different simulated operations may be performed according to the compartment suspected to be involved. In women with anterior zone dysfunction, temporary support of the midurethra or bladder neck may help clarify the anatomical contribution to stress urinary incontinence. In contrast, in patients with posterior compartment symptoms, mechanical support of the vaginal apex or posterior fornix with a speculum, tampon, forceps, or similar maneuver may be more informative. These techniques are intended to mimic the effect of restoring ligamentous support and to determine whether symptom relief can be achieved during examination.

SIMULATED OPERATIONS IN THE ANTERIOR COMPARTMENT

In the anterior compartment, the aim of the simulated operation is primarily to assess the contribution of the pubourethral ligament and related suburethral support structures to stress urinary incontinence. Petros[3] describes this test as being performed with the bladder full, by applying the tip of a finger or an artery forceps unilaterally immediately behind the pubic bone at the site of the pubourethral ligament while the patient coughs. If urine loss is reduced or abolished, the finding supports the view that defective anterior support is contributing to the symptom. This maneuver may also relieve urgency in some women with mixed incontinence and may suppress cough-activated detrusor instability.[5]

A related anterior compartment maneuver is the pinch test (**Figure 2**) in which a unilateral fold of vaginal epithelium is grasped to simulate tightening of the suburethral hammock. Petros[2] notes that this test may completely control stress leakage in a proportion of patients, thereby emphasizing the importance of adequate hammock support for continence. In some women, simultaneous support of both the pubourethral ligament and the hammock almost completely abolishes leakage during coughing, suggesting that combined restoration of these structures may be relevant when planning anterior compartment reconstruction.

The clinical value of anterior compartment simulated operations lies in their ability to convert a static examination into a dynamic functional assessment.[7] Rather than identifying only anatomical laxity, the examiner can directly observe whether restoration of support modifies leakage or urgency. In this way, the test helps connect symptom

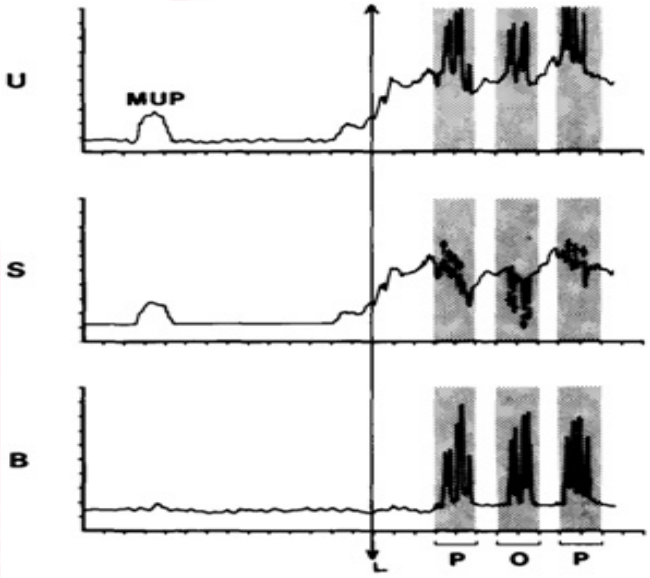

Figure 2. U" indicates the pressure measured in the urethra. "B" indicates the simultaneous pressure measured in the bladder. And "S" indicates the electronically subtracted pressure" U" minus "B". The maximal urethral pressure (MUP) is indicated on the left side of the upper diagram, as measured by a mechanically withdrawn transducer. The transducer was then manually positioned at approximately the mid-urethral point, and the vagina tightened by application of forceps to one side of the urethra approximately one cm proximal to the urethrovesical junction. Compression of vagina was commenced at the vertical line L. Note the increase in MUP on application of the "pinch" just to the right of the vertical line. This may be attributed to more efficient contraction of the slow twitch muscles. The shaded areas indicate application of the "pinch" (P) to the vagina during coughing. release of "pinch" (O). pinch "(again reapplication of "pinch (P). The ratio between the spikes at U and B is the cough transmission ratio (CTR). We attribute the CTR to contraction of the fast twitch muscles. The- "Pinch CTR" is best seen in the subtractor channel, "S" where positive spikes are shown at P, then negative spikes at 0. followed again by positive spikes again at P. These are indicated by small directional arrows.[6]

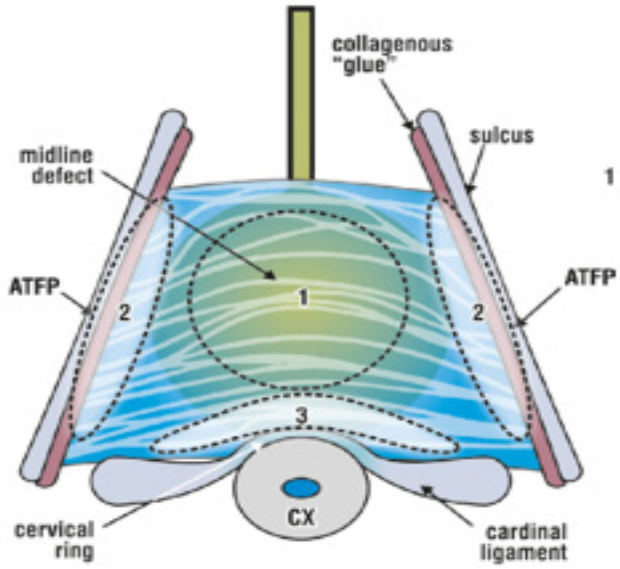

Figure 3. Potential sides for middle compartment defects: 1. Midline defect (central part of pubocervical fascia); 2. Paravaginal defect (collagenous 'glue' and ATFP: Arcus tendinious fascia pelvis); 3. High cystocoele (attachment of pubocervical fascia to cervical ring, 'transverse defect'. Schematic 2D view from below. Perspective: looking into the anterior wall of the vagina[3]

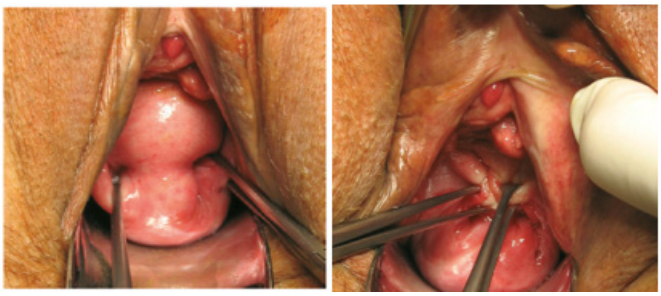

Figure 4. Left: Diagnosing a cardinal ligament/cervical ring defect. The vaginal tissue is grasped in the position of the cardinal ligaments, and approximated medially.[3] **Right:** Disappearance of the cystocoele confirms cardinal ligament/cervical ring defect as the cause of the cystocoele. Persistence of a bulge indicates the cystocoele is central/paravaginal[3]

expression with the anterior zone structures that the Integral Theory identifies as central to continence control, particularly the pubourethral ligament, the suburethral hammock, and, in selected cases, the external urethral ligament.[8]

SIMULATED OPERATIONS IN THE MIDDLE COMPARTMENT

Within the Integral Theory framework, the middle compartment extends from the bladder neck to the anterior cervical ring and includes the arcus tendineus fascia pelvis (ATFP), pubocervical fascia (PCF), and the cardinal ligament/cervical ring complex (**Figure 3, 4**). As there are no transverse ligaments in this zone, the PCF is regarded as the principal supporting structure. Defects in this compartment may occur in the midline, laterally, or at the cervical ring attachment, and correct identification of the damaged structure is considered essential before planning repair.[3]

From a functional perspective, middle zone defects may contribute to cystocele-related dysfunction and may also be associated with storage and emptying symptoms. Petros[3] notes that urgency and frequency may occur with damage in any zone, although they are more commonly linked to posterior zone defects, especially in older women. At the same time, connective tissue laxity in the middle or posterior zones may contribute to detrusor underactivity, overflow symptoms, post-micturition dribble, or even urinary retention. These observations highlight the importance of evaluating the middle compartment not only for prolapse, but also for functional bladder complaints.

In clinical practice, simulated operations in the middle compartment aim to determine whether temporary restoration of support to the PCF or its attachments modifies the patient's symptoms or the visible prolapse pattern. This is particularly relevant in women with cystocele, abnormal emptying, or mixed symptom complexes, where the anatomical contribution of the middle zone may not be obvious from static examination alone. Within the Integral Theory diagnostic system, the pictorial algorithm is used together with examination and simulated operations to localize the likely origin of symptoms more precisely.

A further practical point is that the middle zone is considered one of the most difficult compartments to repair because it is exposed to intra-abdominal pressure from above and gravity from below. For this reason, preoperative localization of whether the defect lies in the central membrane, lateral attachments, or cervical ring attachment is emphasized. In this context, simulated operations may be useful as dynamic bedside tests that strengthen the link between middle compartment anatomy, prolapse configuration, and urinary dysfunction.

SIMULATED OPERATIONS IN THE POSTERIOR COMPARTMENT

Within the Integral Theory framework, the posterior compartment extends from the posterior cervical ring to the perineal body and is closely related to the uterosacral ligaments (USLs), rectovaginal fascia (RVF), and posterior vaginal support structures. This zone is of particular clinical importance, as posterior compartment laxity has been associated with an increased likelihood of a characteristic symptom complex, including chronic pelvic pain, urgency, frequency, nocturia, abnormal bladder emptying, and obstructive defecation. In the pictorial diagnostic algorithm, chronic pelvic pain and nocturia are considered especially suggestive of uterosacral ligament laxity.[3]

Simulated operations in the posterior compartment are designed to determine whether temporary restoration of support to the posterior fornix or vaginal apex leads to symptom relief. In practice, this is most commonly achieved by mechanical support of the posterior fornix with a speculum, tampon, pessary, or similar maneuver.

Among posterior compartment tests, the speculum test is the best known. A gently inserted speculum placed into the posterior fornix may temporarily support lax USLs and the associated visceral nerve plexuses. In selected patients, this maneuver may reduce urgency, pelvic pain, or both.[9,10] The same principle has also been described using other temporary support methods, including a tampon or pessary placed to support the vaginal apex. These maneuvers attempt to reproduce, in a reversible and noninvasive way, the functional effect of posterior ligament repair.

The clinical relevance of this approach has been highlighted in recent literature on posterior fornix syndrome and IC/BPS-like symptoms.

In the Scheffler report, preoperative support of the vaginal apex with a speculum and later with a tampon considerably improved urge and pain before definitive repair. Similarly, the later review by Petros et al.[10] emphasized that posterior fornix syndrome (PFS) should be considered in women with bladder pain, urgency, frequency, nocturia, and abnormal emptying, especially when symptoms improve during temporary support of the posterior fornix. These observations suggest that posterior compartment simulated operations may be particularly informative in women with complex bladder and pelvic pain symptoms that are otherwise difficult to localize anatomically.

From a practical standpoint, posterior compartment testing is valuable because static examination alone may underestimate the functional importance of uterosacral ligament laxity. Some patients may have little or no obvious prolapse, yet still report prominent urgency, nocturia, pelvic pain, or voiding dysfunction. In such cases, symptom improvement during a simulated operation may provide useful clinical evidence that posterior support failure is relevant. This is especially important when evaluating patients with overlapping symptoms, in whom the relationship between anatomy and function is not immediately evident.

CLINICAL INTERPRETATION AND LIMITATIONS OF SIMULATED OPERATIONS

Although simulated operations are a valuable component of the Integral Theory[2] diagnostic system, their findings must be interpreted in the broader clinical context. Symptom improvement during temporary support does not by itself establish a definitive diagnosis, but rather suggests that the tested compartment may be functionally relevant to symptom generation. In this sense, simulated operations should be understood as dynamic clinical tests that complement, rather than replace, history taking, examination, imaging, and other diagnostic investigations.

One of the main strengths of simulated operations is their ability to link symptoms with anatomy in real time. This may be particularly useful in women with overlapping complaints, such as mixed urinary symptoms, chronic pelvic pain, nocturia, or abnormal emptying, where static prolapse grading alone may not explain the clinical picture. By temporarily restoring support and observing whether symptoms improve, the examiner may gain practical insight into which vaginal zone is most likely contributing to the patient's dysfunction.

However, these maneuvers also have important limitations. First, they are inherently examiner-dependent and require familiarity with the anatomical principles of the Integral Theory. Second, patient responses may be subjective, especially when the outcome being assessed is pain, urgency, or sensory relief rather than visible stress leakage. Third, symptom improvement during a simulated operation may reflect partial rather than exclusive involvement of the tested compartment, since many pelvic floor symptoms arise from interacting defects across more than one zone.

Another limitation is that the absence of symptom relief does not necessarily exclude compartmental dysfunction. Some women may have advanced connective tissue damage, coexisting neurological or inflammatory conditions, or central sensitization phenomena that reduce the predictive value of temporary support maneuvers. In addition, the response may vary depending on the technique used, the degree of support achieved, bladder volume, and the symptom being tested. For these reasons, simulated operations should be interpreted as part of a structured diagnostic pathway rather than as isolated stand-alone tests.

Despite these limitations, simulated operations remain clinically attractive because they offer a simple, low-cost, bedside method for functional testing of suspected anatomical defects. In selected patients, especially those with posterior compartment symptoms or mixed pelvic floor complaints, they may provide useful support for diagnostic reasoning and help guide compartment-specific reconstructive planning. Their greatest value may lie not in absolute diagnostic certainty, but in narrowing the anatomical focus of evaluation and making the relationship between support failure and symptom expression more clinically visible.

RELEVANCE OF SIMULATED OPERATIONS IN CONTEMPORARY UROGYNECOLOGICAL PRACTICE

In contemporary urogynecological practice, simulated operations retain particular relevance because they offer a functional approach to symptom assessment at the bedside. While modern evaluation increasingly incorporates imaging, urodynamics, and symptom questionnaires, these tools do not always clarify the relationship between anatomical findings and symptom generation. Simulated operations address this gap by allowing the examiner to test, in real time, whether temporary restoration of support modifies the patient's symptoms. In this respect, they remain consistent with the original aim of the Integral Theory diagnostic system: to connect symptoms, anatomical defects, and treatment strategy within a single clinical framework.

Another advantage of simulated operations is their accessibility. They are low-cost, rapid, and do not require sophisticated equipment, making them especially valuable in settings where advanced diagnostic resources may be limited. As emphasized in the Integral Theory text, the diagnostic algorithm and simulated operations were designed so that a high degree of diagnostic accuracy could be achieved at the clinical level without reliance on expensive technology. This gives the method continued practical value, particularly in resource-limited settings or in the initial evaluation of women with pelvic floor complaints.

At the same time, their place in modern practice should be viewed as complementary rather than competitive. Simulated operations are unlikely to replace imaging, cystoscopy, or urodynamics where these are indicated, but they may enrich interpretation by adding a dynamic and symptom-oriented dimension to clinical examination. Their contemporary value lies in helping the clinician move beyond static compartment description toward a more functional understanding of pelvic floor disorders. In this way, simulated operations continue to offer a clinically useful bridge between anatomical theory and individualized patient assessment.

CONCLUSION

Urogynecological examination within the Integral Theory framework offers a structured and functional method and emphasizes the dynamic relationship between connective tissue support and symptom generation. In particular, simulated operations provide a practical bedside means of testing whether temporary restoration of support modifies clinical symptoms.

In contemporary practice, simulated operations remain relevant not as replacements for modern diagnostic tools, but as complementary functional tests that can refine clinical reasoning and support compartment-specific management. Their continuing value lies in helping clinicians connect anatomy, symptoms, and treatment planning in a more integrated and individualized way.

ETHICAL DECLARATIONS

Peer Review Process

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Conflict of Interest

The author declare no conflicts of interest.

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Author Contributions

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I was born in Trabzon, in 1985. After completing my primary and secondary education in my hometown, I graduated from medical school with a fourth degree from Marmara University School of Medicine in English with a 2010. I then completed my residency training in Obstetrics and Gynecology between 2011 and 2015 at Zekai Tahir Burak Women's Health Education and Research Hospital. For my compulsory medical duty; I had worked at Şanlıurfa Training and Research Hospital for ten years. During this period I had worked as a chief physician of the hospital for two years and chief of the clinics for four years. At 2023, I achieved the degree of Associate Professor. I moved my hometown, Trabzon, in 2025 March. I have been working at Trabzon University Kanuni Training and Research Hospital since March 2025. During my career especially in Şanlıurfa, I was interested in maternal mortality, neonatal mortality improvement studies of Ministry of Health. I am also an inspector in clinical audit of mother-friendly hospitals in Turkey working with the Ministry of Health. I am interested in high-risk pregnancies especially diagnosing and the treatment of placenta adhesion spectrum disorders and urogynecology. Throughout my career, I have authored approximately 50 national and international scientific publications. Additionally, I have delivered numerous oral and poster presentations at various national and international scientific meetings. I am working as section editor and reviewer positions in both national and international journals. I am also a member of Royal College of Obstetrics and Gynecology (RCOG).

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Chickenpox infection in adolescents

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ABSTRACT

Varicella-zoster virus (VZV), a member of the herpes virus family, mostly causes chickenpox infection in childhood and shingles in adulthood. Chickenpox has a high risk of transmission and severe viremia. It can lead to serious morbidity and even death in children. The chickenpox vaccine is produced in human diploid cell culture and can be safely administered even in those with severe egg allergy. A history of anaphylactic reaction to any of the vaccine components is an absolute contraindication. Other important contraindications for vaccination include pregnancy, immunodeficiency, use of immunosuppressive drugs, and active tuberculosis. The chickenpox vaccine can be administered concurrently with other childhood vaccines. If the vaccines to be administered are live parenteral vaccines, they should be administered on the same day or 28 days apart. If a PPD screening test is to be performed for tuberculosis diagnosis, it is recommended that the vaccine be administered on the same day and the test read 48-72 hours later. Concurrently with the chickenpox vaccine; If immunoglobulin, blood, or blood products are required, vaccination should be postponed. If vaccination has already been given, it should be repeated after the prescribed time, depending on the type and amount of product used. Since the VZV is susceptible to acyclovir, valacyclovir, and famciclovir, these antiviral drugs should be used one day before or 14 days after vaccination. Those working in crowded environments, including healthcare facilities, schools, child and elderly care centers, university students, military and security personnel, and teachers, are at risk of chickenpox infection and should definitely be vaccinated against chickenpox. Vaccination is the easiest and most reliable way to protect against chickenpox and shingles. Studies in countries where the vaccine is administered have shown significant reductions in chickenpox cases and the economic burden of the disease. In some countries, it has been reported that a single dose of the chickenpox vaccine provides high protection against moderate to severe chickenpox infection, but chickenpox cases are rarely seen after vaccination. A two-dose vaccine administration, however. It has been observed that it provides good protection against all forms of the disease, prevents transmission, and creates a high level of herd immunity. Therefore, we recommend restarting the two-dose vaccine administration in the national vaccination program implemented in our country.

Keywords: Chickenpox, herpes zoster, vaccination in adolescence

INTRODUCTION

The varicella-zoster virus (VZV) typically causes two different clinical presentations: chickenpox infection of varying severity in childhood and shingles infection in adults. The virus enters the body through respiratory secretions, vesicular fluid, or direct contact with lesions.[1,2] In children, the disease manifests with fever and a widespread vesicular rash. With these characteristics, chickenpox has a high risk of transmission and severity of disease. As the child gets older, the disease becomes more severe and the risk of complications increases. Although it can be mild in childhood, severe clinical presentations and death can occur. In adults, varicella-zoster settles in the dorsal nerve ganglia; reactivation of the virus causes vesicular lesions to appear in dermatome areas; this is a clinical condition known as shingles.[3]

Chickenpox is usually not severe, but it can increase the risk of hospitalization and death in adolescents and adults. It can also lead to conditions such as pneumonia and encephalitis. Approximately 90% of unvaccinated household members of an infected person contract chickenpox. The risk of contracting chickenpox is higher in people who are in close contact, such as school-aged children, students in other institutions, and those in crowded environments.[4]

CHICKENPOX

Epidemiology, Symptoms, and Risk Factors of Chickenpox

The most distinctive symptom of chickenpox is a rash consisting of itchy blisters that appear all over the body. The rash may spread to the mouth, other parts of the body, or the scalp. Chickenpox can also cause body aches, fever, and fatigue.[4,5]

In the United States (US), prior to the introduction of routine vaccination, there were four million cases of chickenpox annually; of these, 10,000 required hospitalization due to

complications, and approximately 100 resulted in death.[4] In our country, studies reporting the complications of chickenpox at the population level are extremely limited. A study conducted in İzmir reported that the risk of hospitalization for any complication among those who had contracted chickenpox was 6.3 per 100,000.[3] In a study conducted by Dinleyici et al.[5] across 27 centers in 14 provinces in our country between 2008 and 2010, it was reported that 824 children were hospitalized due to chickenpox complications, and 604 (73.3%) of these were previously healthy children with no underlying medical conditions. All susceptible patients in the hospital are at risk of infection.[6-9]

Prevalence of Chickenpox

There are numerous studies in the literature regarding the prevalence of chickenpox. In a study conducted in Spain in 2008 involving 1,324 children, the seroprevalence of chickenpox was found to be 82% among 5-9-year-olds, 91.1% among 10-14-year-olds, and 94.9% among 15-24-year-olds.[7] In a study by Ronan et al.,[7] approximately 70-80% of adolescents who reported not having had chickenpox were found to be positive for chickenpox antibodies. In a study by Kanra et al.,[8] 80% of university students with no history of chickenpox were found to be positive for chickenpox antibodies.

CHICKENPOX VACCINE

The VZV vaccine, which contains a live attenuated virus, was derived from the OKA strain by Dr. Takahashi[11] at the Biken Institute in Osaka, Japan, in 1974. Currently, the monovalent vaccine produced from the OKA strain was first approved in Japan in 1987 and received a license in 1995 for use in healthy individuals aged 12 months and older who have not previously had the disease. All chickenpox vaccines are licensed for use in children aged 12 months and older. The recommended vaccination schedule for children involves two doses: the first dose between 12 and 15 months of age and the second dose between 4 and 6 years of age; however, in our country, the national vaccination schedule involves a single dose administered at 12 months of age. In particular, pregnant women, infants born to mothers who are not immune to chickenpox, those born before 28 weeks' gestation or weighing less than 1,000 grams (regardless of the mother's immune status), and those with immunodeficiency are at risk of severe varicella infection and complications. Those with no history of chickenpox or where there is uncertainty regarding their history should be considered susceptible; all healthcare staff should be vaccinated.[6-9]

Adverse effects following the varicella zoster vaccine include pain and redness at the injection site, fever, a rash near the injection site, a widespread rash over the body, herpes zoster infection, anaphylaxis, encephalitis, ataxia, erythema multiforme, Stevens-Johnson syndrome, pneumonia, thrombocytopenia, convulsions, neuropathy, and Guillain-Barré syndrome.[9-11]

Contraindications for Vaccination

As the varicella vaccine is produced from human diploid cell cultures, it can be administered safely even in individuals with severe allergies to eggs or egg proteins.[12-15] The vaccine is contraindicated in those with a history of anaphylactic reactions to any of its components (neomycin, gelatine, etc.) and during pregnancy.[15] For individuals with hematological malignancies, solid tumors, or those undergoing active chemotherapy; those with congenital or acquired T-lymphocyte disorders; those who have undergone solid organ or hematopoietic stem cell transplantation; and those using biological agents for autoimmune conditions, those using IL-1 receptor antagonists (anakinra), tumor necrosis factor-alpha inhibitors (etanercept, infliximab, and adalimumab) and anti-CD20 agents (rituximab), as well as those using immunosuppressive agents, and those receiving long-term high-dose systemic glucocorticoid therapy (such as those taking 2 mg/kg or more of prednisone or equivalent per day, or 20 mg/day of prednisone or equivalent for more than 14 days) in situations that may cause severe immunodeficiency, vaccination is contraindicated. The vaccine should also not be administered to those with untreated active tuberculosis.[15-17]

Points to Note Regarding Vaccination

The varicella vaccine can be administered at the same time as other childhood vaccines. If they cannot be administered simultaneously, there must be an interval of at least 28 days between the varicella vaccine and other live virus vaccines administered via a similar route. If a PPD screening test is to be performed, the recommended method is to administer the varicella vaccine on the same day and read the test 48–72 hours later. If they cannot be administered on the same day, there must be a 28-day interval between the test and vaccination. The varicella vaccine must be postponed for varying periods, depending on the type and dose of the immunoglobulin, blood, and blood products administered, as is the case with the measles vaccine. The varicella vaccine virus is sensitive to acyclovir, valacyclovir, and famciclovir; these antiviral agents should be avoided from one day before to 14 days after the day the vaccine is administered.[14] For those planning a pregnancy, it is recommended to wait at least four weeks after vaccination. Given the very low transmissibility of the vaccine virus, the high likelihood of the pregnant woman being immune, and the benefit of vaccination in reducing the risk of transmission, it is considered appropriate to administer the varicella vaccine to children living in the same household if there is a pregnant woman in the home.[19] Although it is not known whether Reye's syndrome is caused by the administration of salicylates following varicella vaccination, the vaccine manufacturer recommends that salicylates should not be used for at least six weeks after the VZV vaccine.[13,18,19]

Who should have the Chickenpox Vaccine Outside of the Routine Childhood Schedule?

All young people and adults who lack chickenpox vaccination or have never had the disease, including those who are unsure, and adults at higher risk of exposure, such as those working in healthcare settings, schools, or childcare centers, as well as university students, teachers, and nursery staff, are included among those in communal work environments. to appear in dermatome areas; this is a clinical condition known as shingles.[3,18,19]

CONCLUSION

As a result, routine vaccination programs in early childhood are cost-effective in terms of societal impact and healthcare efficiency. Because the specific costs and epidemiological conditions related to varicella vaccination vary significantly between countries, it is not possible to extrapolate results from one country to another. Therefore, country-specific sociodemographic and economic analyses are necessary.

In countries where the varicella vaccine is included in routine vaccination programs, efficacy studies have shown a significant reduction in varicella and shingles infections in adults, as well as a significant decrease in the economic burden associated with the disease. Scientific studies have shown that a single dose of the varicella vaccine provides high protection against moderate to severe varicella infection. However, for optimal protection against all forms of varicella, two doses are crucial; this prevents transmission, reduces new cases and the risk of outbreaks, and is of great importance in achieving herd immunity. The expected benefits of two doses of varicella vaccination can be expressed as a decrease in the incidence and complications of varicella, a decrease in the number of susceptible individuals, prevention of varicella disease despite vaccination, prevention of varicella outbreaks, and a decrease in the circulation of the wild-type virus. For all these benefits, we recommend that two doses of vaccine be reintroduced into the childhood vaccination schedule as part of our national immunization program.

ETHICAL DECLARATIONS

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This review was externally peer-reviewed.

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The author declare no conflicts of interest.

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I was born in Ankara in 1969. I completed my primary, secondary, and high school education in Ankara. In 1994, I graduated from Eskişehir Osmangazi University Faculty of Medicine. In 2001, after completing a four-year pediatrics training program at the Ministry of Health Dr. Sami Ulus Children's Health and Diseases Training and Research Hospital, I became a specialist in Child Health and Diseases. Due to my mandatory state service, I worked at Aksaray Ortaköy State Hospital. In 2016, I was appointed as a faculty member at Ankara Yıldırım Beyazıt University Faculty of Medicine. In 2019, I completed my Master's degree in Social Pediatrics at Ankara University Faculty of Medicine. I received the title of Associate Professor in 2020. In 2020, I started working at Ankara Bilkent City Hospital. I received the title of Professor in 2025. I retired at the end of 2025 and simultaneously started working at Üsküdar University Faculty of Medicine.