Research Article

Serum Vitamin D Levels, Visual Analog Scale Dysmenorrhea Score, and Endometriosis ASRM Classification: a Relationship Study

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Abstract

Objective: To assess the correlation between vitamin D levels, dysmenorrhea intensity measured by the visual analogue scale (VAS), and the stage of endometriosis determined by the American Society of Reproductive Medicine (ASRM) grading score.

Methods: A cross-sectional study was conducted involving 37 women diagnosed with suspected endometriosis who met the inclusion and exclusion criteria. The aim was to determine the correlation between vitamin D levels, dysmenorrhea VAS scores, and the ASRM endometriosis stage at RSUP Dr. Mohammad Hoesin Palembang from November 2021 to April 2022. Bivariate analysis was employed to assess correlation, utilizing Pearson's correlation test and the Spearman Rank correlation test as an alternative method.

Results: There was a significant positive correlation between vitamin D levels and the VAS score for dysmenorrhea (r = 0.678; p = 0.000) and a very strong positive correlation between vitamin D levels and the degree of endometriosis (r = 0.774; p = 0.000) based on Spearman Rho's correlation test.

Conclusion: There is a significant relationship between vitamin D levels with the VAS score of dysmenorrhea and the degree of endometriosis ASRM.

Keywords: american society of reproductive medicine, endometriosis, visual analogue scale, vitamin D.

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INTRODUCTION

Endometriosis, an estrogen-dependent gynecologic disease, is characterized by the presence of endometrial functional tissue (endometrial glands and stroma) implanted ectopically outside the uterine cavity. It affects thirty-five to fifty percent of reproductive-age women, although many cases are suspected to be underdiagnosed. Commonly reported symptoms include dysmenorrhea, infertility, or both.[1] Some women experience severe pain, with prevalence varying from 3% to 33%, which can be incapacitating for 1-3 days, significantly impacting their ability to move. Consequently, these complaints often greatly affect the patient's quality of life.[2,3]

Increased concentrations of PGE2 and PGF2α which are higher in the menstrual fluid of patients with dysmenorrhea are thought to be the most

potent cause of pain, especially PGF2α. Until now, the etiology of endometriosis itself is still unclear, but several studies have suggested the possibility of an influence on vitamin D levels. Previous studies have also suggested that there is a strong association between vitamin D deficiency and other factors, which determines a wide range of polymorphic clinical manifestations where menstrual disorders are important in pubertal women. Vitamin D receptors and 1α-hydroxylase enzymes, responsible for catalyzing the formation of D3 from its precursor, 25(OH)D, are expressed in the uterus and immune system cells. This presence leads to the belief that vitamin D may offer benefits in preventing uterine abnormalities.[4]

Vitamin D is a group of fat-soluble steroids derived from cholesterol. Vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol) are the two main forms of vitamin D. Vitamin D can work after binding to its receptors (vitamin D receptors or VDR) which are located throughout the body, including blood vessels and reproductive tissues, such as the uterus, ovaries, and placenta. The existence of VDR in reproductive tissue makes many hypotheses that vitamin D has a relationship with endometriosis.[5,6] In further research, it is known that vitamin D has a role in reducing the severity of endometriosis, thereby reducing the degree of the pain by lowering pro-inflammatory cytokine levels and prostaglandin biological activity.[6]

Another factor, activity, and body mass index (BMI) was known to be associated with dysmenorrhea and the degree of endometriosis. The level of activity also had a strong and significant positive correlation with the VAS dysmenorrhea score and the degree of endometriosis. Physical activity increases systemic levels of various cytokines with anti-inflammatory properties. Striated muscle is identified as an endocrine organ, which through contraction, stimulates the production and release of myocytokines, which can influence and alter metabolism and cytokine production in tissues and organs. Evidence suggests that symptoms associated with endometriosis result from localized peritoneal inflammatory reactions caused by ectopic endometrial implants. Regular physical exercise appears to have a protective effect against diseases involving inflammatory processes as it induces an increase in systemic cytokine levels with anti-inflammatory and antioxidant properties and acts by reducing estrogen levels.[7]

While with BMI, although previous studies have shown that there no association between BMI and the degree of dysmenorrhea[8] and the incidence of endometriosis[9], higher BMI is often associated with chronic inflammation, which could be a contributing factor in both pain and discomfort associated with dysmenorrhea and endometriosis potentially worsen the. Obesity is also often associated with lower levels of physical activity.[10] Reduced physical activity can lead to decreased endorphin release, which might affect pain perception during dysmenorrhea. Also higher BMI associated with increased prostaglandin production which plays a role in uterine contractions and menstrual pain.[11]

Therefore, this study aimed to analyze the correlation between serum vitamin D levels and the intensity of dysmenorrhea, measured using the *visual analogue scale* (VAS), as well as the stage of endometriosis, determined by the American Society of Reproductive Medicine (ASRM) grading score. In addition, this study also assessed the relationship between body mass index (BMI) and activity on the VAS score of dysmenorrhea and the degree of endometriosis.

This comprehensive investigation into the relationship between endometriosis, dysmenorrhea, vitamin D, and additional factors such as activity and BMI aims to explore the potential impact of vitamin D on the severity of endometriosis and its symptoms. By delving into these interactions, this study endeavors to offer valuable insights into an area that remains incompletely understood, thereby contributing to a deeper comprehension of the involved mechanisms.

METHODS

A cross-sectional study was carried out to examine the correlation between serum vitamin D levels with dysmenorrhea VAS scores and endometriosis ASRM in RSUP Dr. Mohammad Hoesin Palembang in the period November 2021 to April 2022. The sample consisted of 37 women who were diagnosed with suspected endometriosis and planned for a laparotomy or laparoscopic procedure. The sample size was determined using the correlation coefficient from a study conducted (0.783),[12] and the formula for correlation calculation was used to establish the sample size. The formula included a 99% level of significance and 99% statistical power. Samples were selected using total sampling

according to the day the patient was diagnosed with endometriosis. The inclusion criteria for this study encompassed women between the ages of 18 and 50 years, diagnosed with endometriosis based on intraoperative findings corroborated by anatomical pathology examinations, who had not undergone hormonal therapy, and expressed willingness to participate in the study. Conversely, individuals with a recent history of vitamin D intake within the last 2 weeks, a medical history of malignancy, kidney disease, or those currently pregnant were excluded from participation.

The concentration of Vitamin D was measured by RSMH laboratory using the ELISA method using a blood sample of up to 5 mL drawn from the cubital fossa vein. The results were categorized into normal (> 30 ng/mL), insufficiency (21 – 29 ng/mL) and deficiency (< 20 ng/mL).[13] While the degree of dysmenorrhea was measured with VAS score by using visual pain assessment tools, in the form of a 10 cm line equipped with an illustration of facial expressions when experiencing pain. The scores were categorized into no pain (0), mild (1-3), moderate (4-6), severe (7-9) and very severe (10).[14] On the other hand, the American Society for Reproductive Medicine (ASRM) classification was used to determine the staging of endometriosis and were classified into grade I (score 1-5), II (score 6-15), III (score 16-40) and IV (score > 40).[15]

The statistical analysis was conducted using SPSS version 20. Bivariate analysis was done to evaluate the correlation between vitamin D levels and dysmenorrhea VAS scores. Regarding the correlation between vitamin D levels and the endometriosis ASRM grading score, the analysis involved the Pearson correlation test, complemented by the Spearman Rank correlation test as an alternative. All analyses were conducted using a 95% confidence interval.

RESULTS

Thirty-seven women participated in the study, ranging in age from 22 to 48 years, with an average of 34.41 ± 6.86 years, and an average BMI of 24.12 ± 3.34 kg/m2 (range 18.2 – 31.2 kg/m2). In addition, as many as 67.6% of patients experienced infertility and 32.4% of them were not infertile (Table 1).

Table 1. Demographics, Clinical and Laboratory Characteristics

Characteristic	Total (n)	(%)
Age		
Mean ± SD	34.41 ± 6.86	
Median	33	
Min-Max	22 – 48	
Body Mass Index (kg/m²)		
Mean ± SD	24.12 ± 3.34	
Median	23.5	
Min-Max	18.2 – 31.2	
Body Mass Index		
Underweight	1	2.7
Normoweight	22	59.5
Overweight	12	32.4
Obese class I	2	5.4
Surgery		
Laparoscopy	31	83.8
Laparotomy	6	16,2
Parity		
Infertile	25	67.6
Non-infertile	12	32.4
Vitamin D (ng/ml)		
Mean ± SD	19.08 ± 7.05	
Median	17.6	
Min-Max	7.4 – 33.1	
Deficiency	25	67.6
Insufficiency	8	21.6
Normal	4	10.8
VAS		
Mean ± SD	4.43 ± 1.66	
Median	5	
Min-Max	2 – 8	
VAS Score		
Mild	13	35.1
Medium	19	51.4
Severe	5	23.5
Endometriosis Degrees		
Grade I	2	5.4
Grade II	2	5.4
Grade III	3	8.1
Grade IV	30	81.0
Activity		
Low	19	51.4
Medium	13	35.1
High	5	13.5

The study revealed a significant prevalence of vitamin D deficiency among endometriosis patients, affecting 67.6% of the sample, with an average vitamin D level of 19.08 ± 7.05 ng/ml (range 7.4 – 33.10 ng/ml). The majority of participants reported moderate VAS scores for dysmenorrhea (51.4%), with an average VAS score of 4.43 ± 1.66 (score range 2 – 8). Furthermore, the study indicated a high prevalence of grade IV endometriosis cases (81.1%) within the sample, and most participants engaged in light physical activity on a daily basis (51.4%) (Table 1).

The results of the Spearman Rho's correlation test revealed a significant positive correlation between vitamin D levels and the VAS score for dysmenorrhea (r = 0.678; p = 0.000, Table 2) and a very strong positive correlation between vitamin D levels and the degree of endometriosis (r = 0.774; p = 0.000, Table 3). This implies that patients with vitamin D deficiency tended to experience more severe dysmenorrhea symptoms and a higher degree of endometriosis, while those with normal vitamin D levels had milder dysmenorrhea and less advanced endometriosis

Table 2. Correlation of vitamin D Levels with VAS Dysmenorrhea Scores

Characteristic	VAS score			*P-value*	r
	Mild	Medium	Severe		
Vitamin D, n (%)				0.001*	0.678
Deficiency	4 (100)	0 (0)	0 (0)		
Insufficiency	6 (75.0)	2 (25.0)	0 (0)		
Normal	3 (23.1)	17 (68.0)	5 (20.0)		

Spearman Rho's test, *p < 0.05

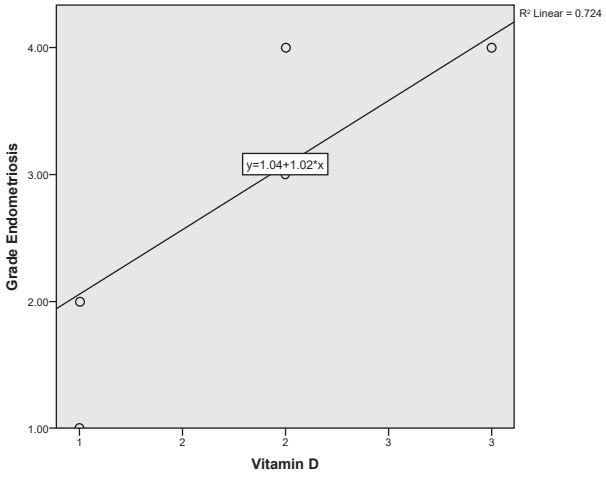

Figure 1. Graph of the correlation of vitamin D with the VAS score

Table 3. Correlation of vitamin D Levels with Degree of Endometriosis

Characteristic	Degree of endometriosis				*P-value*	r
	Grade I	Grade II	Grade III	Grade IV		
Vitamin D, n (%)					0.000*	0.774
Deficiency	2 (50.0)	2 (50.0)	0 (0)	0 (0)		
Insufficiency	0 (0)	0 (0)	3 (37.5)	5 (62.5)		
Normal	0 (0)	0 (0)	0 (0)	25 (100)		

Spearman Rho's test, *p < 0.05

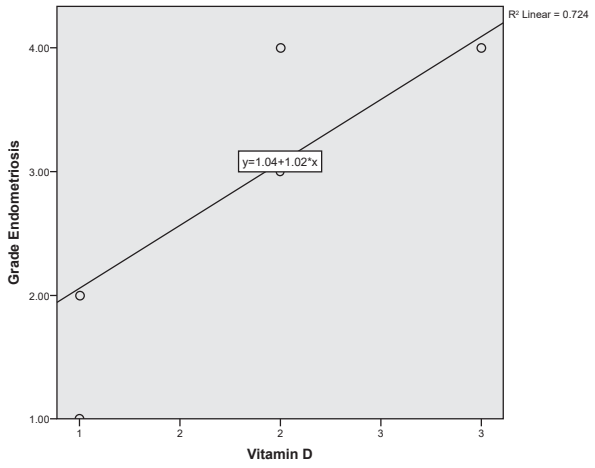

Figure 2. Graph of the correlation of vitamin D with degree of endometriosis

The results of the study, as shown by the Spearman Rho's test (Table 4), shed light on the relationship between body mass index (BMI), physical activity, and the degree of endometriosis and the severity of dysmenorrhea. Notably, the correlations between BMI and these parameters were found to be weak and insignificant, with a positive correlation coefficient of 0.259 for dysmenorrhea VAS score and 0.176 for the degree of endometriosis. In contrast, the relationship between physical activity and these variables was more pronounced and significant. The study demonstrated a strong and significant positive correlation between activity and dysmenorrhea VAS scores (r = 0.638; p = 0.000) and a moderate and significant positive correlation between activity and the degree of endometriosis (r = 0.536; p = 0.001). These findings suggest that higher levels of physical activity are associated with milder dysmenorrhea symptoms and a lower degree of endometriosis and vice versa, while BMI has a limited impact on these parameters in this study group.

Table 4. Correlation between Body Mass Index with VAS Score and Degree of Endometriosis

Variabel	Variabel	N	r	*P-value*
Body Mass Index Activity	VAS score	37	0.259	0.176
	Degree of endometriosis	37	0.176	0.299
	VAS score	37	0.638	0.000*
	Degree of endometriosis	37	0.536	0.001*

Spearman Rho's test, *p < 0.05

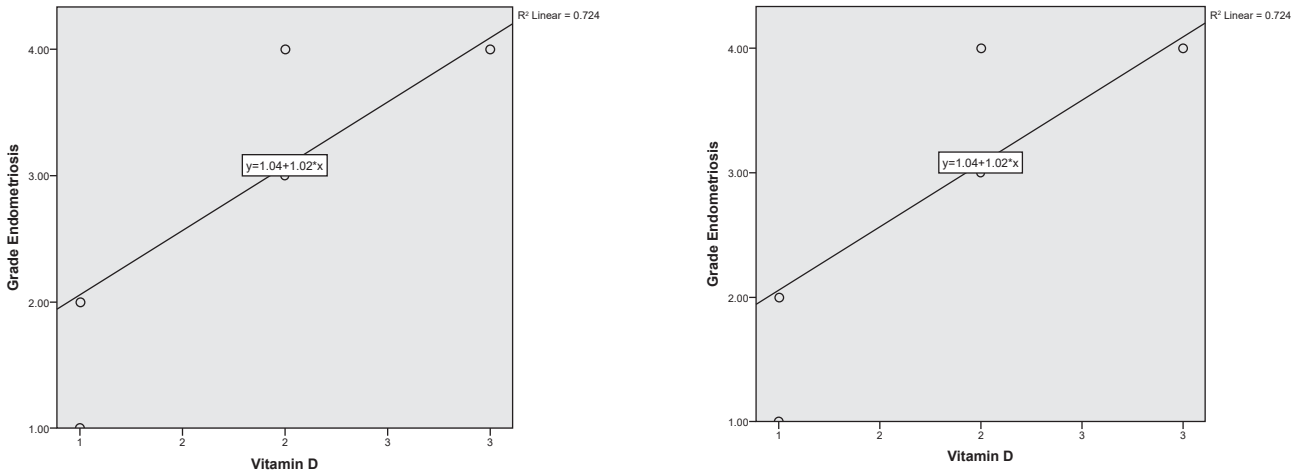

Figure 3. Correlation between Body Mass Index with VAS Score and Degree of Endometriosis

DISCUSSION

In this study, 37 women were involved, and the mean age of endometriosis patients was 34.41 ± 6.86 years (range 22 – 48 years). This is in line with the study which found that the average age of endometriosis patients was 34.22 ± 6.54 years (range 18 – 45 years).[16] These results were not much different from where the average age of the patients was obtained. endometriosis in the two treatment groups in their study amounted to 33.4 ± 0.892 years and 34.7 ± 0.925 years.[17] Similarly, a study reported an average age of endometriosis patients of 33.3 ± 6.23 years.[18]

In this study, most endometriosis patients had a normoweight body mass index (59.5%) with an average BMI of endometriosis patients in this study of 24.12 ± 3.34 kg/m^2 (range 18.2 – 31.2 kg/m^2). Another study found similar results which reported endometriosis patients BMI was reported to be 23.48 ± 1.90481.[19] The average BMI of endometriosis patients ranged from 22.46 to 23 kg/m^2.[20] A greater average BMI of 27.1 ± 0.752 kg/m^2 and 27.8 ± 0.710 kg/m^2.[11] Research found a lower mean BMI of 21.1 (15.2–33.5 kg/m^2) and reported no difference in mean BMI between endometriosis patients and healthy controls ($p > 0.05$).[9]

In this study, 67.6% of endometriosis patients had vitamin D deficiency, with an average vitamin D level of 19.08 ± 7.05 ng/ml (range 7.4 – 33.10 ng/ml). Vitamin D receptor expression was found to be significantly lower in samples from endometriosis patients than in samples from normal endometrium in both the proliferative phase (12.88% vs 20.12%) and the secretory phase (10.32%; 21.51%), according to research ($p < 0.05$). Vitamin D could be used as a targeted therapy for endometriosis seeing as vitamin D deficiency plays a significant role in its pathogenesis. Research has suggested several possible reasons for lower vitamin D levels in endometriosis patients, one of them is dietary habits. Previous studies have shown that a higher intake of dairy products and 1,25-dihydroxy vitamin D3 is associated with a decreased risk of endometriosis.[21]

One of the most prevalent complaints in women with gynecologic problems is dysmenorrhea, including endometriosis. The visual analogue scale (VAS) was used in this study to quantify the pain associated with endometriosis. The results showed that most endometriosis patients complained of moderate pain (51.4%). According to the VAS score, it was also observed that patients with vitamin D deficiency tend to experience moderate to severe pain. Vitamin D has a very strong correlation with dysmenorrhea pain in endometriosis patients, where the more deficient levels of vitamin D, the more severe the pain is felt. The association between vitamin D levels and dysmenorrhea lies in the pathogenesis of dysmenorrhea, where prostaglandins are released from endometrial cells. Vitamin D and vitamin D receptors work on many organs, one of which is the endometrial cells, and play an important role in reducing the production of prostaglandins.[22]

In this study, there were differences in vitamin D levels based on dysmenorrhea pain scores. This may be due to vitamin D regulating the immune system in chronic inflammatory responses. Inflammatory processes can influence the metabolism of vitamin D and may lead to lower vitamin D levels in individuals with more severe menstrual pain. With Vitamin D supplementation, the production of anti-inflammatory cytokines is increased and that of pro-inflammatory cytokines is decreased.[20] The active form of vitamin D, calciferol, also known to control prostaglandin production.[23]These results are in line with research which involved 372 women reporting a negative correlation between serum 25(OH)D levels and pain index ($r = -0.612$; $p = 0.044$). Most of women with mild dysmenorrhea (VAS score 1 -3) have vitamin D insufficiency, meanwhile those with moderate dysmenorrhea (VAS score 4-7) have vitamin D deficiency.[6] Furthermore, several studies compared vitamin D levels and VAS score in groups which given vitamin D supplementation and groups given a placebo or no intervention. The results in the group given vitamin D supplementation had a significantly lower VAS score.[1,14,24] Vitamin D supplementation reduced pain intensity with a reduction of 1.0 score at week 4 and 1.5 scores at week 8 ($p< 0.001$).[25] A clinical trial comparing the effects of vitamin D administration with a placebo on the VAS score of patients with endometriosis who had undergone laparoscopy. The findings reported that giving vitamin D to patients who had undergone ablative surgery had no discernible effect.[20]

Vitamin D exhibits a notable correlation with the degree of endometriosis. This study revealed discernible differences in vitamin D levels corresponding to the severity of endometriosis, indicating a robust and significant negative

correlation between vitamin D levels and the degree of endometriosis. Lower vitamin D levels were consistently associated with more severe degrees of endometriosis, aligning with findings from a meta-analysis demonstrating a negative correlation between vitamin D status and disease severity (stage III–IV vs stage I–II: SMD − 1.33 ng/mL, 95% CI − 2.54 to − 0.12; p=0.03). Numerous additional studies have also indicated a similar relationship between vitamin D levels and the severity of endometriosis in affected women.[12,26,27] In vitro and animal studies have suggested that vitamin D supplementation leads to regression of endometriotic implants, decreased invasion, and reduced proliferation.[28] The role of vitamin D in inhibiting cell proliferation can be explained by understanding the role of vitamin D in the cell cycle. The vitamin D 1,25(OH)2D3-VDR system stops the cell cycle at the G0-G1 transition through several mechanisms. 1,25(OH)2D3 activates VDR directly by binding to the p21 promoter and inducing its expression. 1,25(OH)2D3 also increased the expression of p15, p16, p18, and p27 which had an impact on cell inhibition, especially the transition phase from G1 to S. Therapy with 1,25(OH)2D3 could inhibit cell proliferation. Microarray analysis demonstrated the upregulation of several genes that regulate the cell cycle, including the kinase 1-activated p21 and p53. Therefore, vitamin D is considered to play a strong role in cell differentiation and proliferation through direct regulation of the cell protein cycle.[29]

Most endometriosis patients in this study did light physical activity (51.4%). Based on the correlation test, activity and VAS scores showed a strong and significant positive correlation. This result is in line with the study that reported a strong correlation between physical activity and dysmenorrhea (p = 0.000; r = -0.650). In addition, physical activity also correlates with the degree of endometriosis, patients with mild physical activity tend to have a severe degree of endometriosis and vice versa. Exercise was known as a non-specific pain relief method by enhancing blood flow in the pelvic region and triggering the release of beta-endorphins. It contributes to the prevention and alleviation of dysmenorrhea by reducing stress levels and improving mood. Exercise also lowers body fat, which is linked to a higher prevalence of dysmenorrhea.[30]

A cross-sectional study involving 1009 participants with endometriosis indicated that pain symptoms could potentially be alleviated by exercise performed the day before. Those who engaged in physical activity at least three times a week tended to report reduced pain symptoms. Conversely, a systematic review, encompassing 3 clinical trials and involving 109 participants, aimed to explore the association between exercise and endometriosis symptoms. The physical activities provided encompassed flexibility and strength training, cardiovascular fitness, and yoga, conducted independently one to four times a week for durations of 8-24 weeks without supervision. However, due to heterogeneity and various confounding factors, a meta-analysis could not be conducted in this study. Consequently, further investigation is required to comprehensively understand the relationship between exercise and its impact on endometriosis symptoms.[31]

CONCLUSION

In this study, serum vitamin D levels exhibited a significant positive strong correlation with the VAS dysmenorrhea score (r = 0.678; p = 0.000), along with a very strong positive correlation with the degree of ASRM endometriosis (r = 0.774; p = 0.000). To enhance our comprehension of the complex interplay among serum vitamin D levels, dysmenorrhea, and endometriosis, future research should prioritize several key areas. Primarily, addressing the limitation of the current study's relatively small sample size is crucial. Conducting research with a larger and more diverse participant pool would enhance the generalizability and robustness of the findings. Longitudinal studies tracking changes in these variables over time would elucidate causality and the dynamic nature of these relationships. Furthermore, investigating additional potential confounding variables, such as dietary practices, lifestyle factors, and other health-related aspects, could offer nuanced insights into these associations. Moreover, employing random sampling strategies instead of patient selection based on the day of diagnosis would mitigate bias in participant selection, resulting in a more representative cohort of women affected by endometriosis. This adjustment would ultimately yield more precise and valuable outcomes for future research endeavors.

LIMITATION of STUDY

The limitation of this study is based on a relatively

small sample size of 37 women, which may limit the generalizability of the findings. A larger and more diverse sample would provide a more comprehensive understanding of the correlation between serum vitamin D levels, dysmenorrhea, and endometriosis. Also, because the sample was selected using total sampling on the day of endometriosis diagnosis. This could introduce selection bias, as patients diagnosed on specific days may not represent the broader population of endometriosis patients. The study design is also cross-sectional, which only allows for the observation of correlations at a single point in time. Longitudinal or prospective studies could provide insights into how these variables change over time and potentially establish causality.

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