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Original Article

Distribution of gynecological pathologies accompanying perimenopausal and postmenopausal adenomyosis

Ozgur Hilal Erinanc[1], Eser Colak[2]

[1]Department of Pathology, Faculty of Medicine, Konya Medical and Research Center, Baskent University, Konya, Turkey
[2]Department of Gynecology and Obstetrics, Faculty of Medicine, Konya Medical and Research Center, Baskent University, Konya, Turkey

Abstract

Aim: To determine the gynecological pathologies accompanying perimenopausal (PEM) and postmenopausal (PM) adenomyosis and to determine which of these pathologies may contribute to the etiology of adenomyosis.

Materials and Methods: We retrospectively reviewed pathology report archives from between 2008 and 2018 and identified surgical hysterectomy specimens that were histopathologically diagnosed as cases of adenomyosis and the accompanying gynecological pathologies. Data regarding medical history were obtained from patient files. The patients were divided into two groups, PEM and PM, and they were compared.

Results: There were a total of 212 patients (154 PEM and 58 PM) diagnosed with adenomyosis by histopathological examination of hysterectomy specimens. The most common complaints in the PEM patients were abnormal uterine bleeding and pelvic pain, and adenomyosis was frequently diagnosed incidentally in the PM women who underwent hysterectomy due to prolapse. The most common concomitant pathology among all patients was uterine leiomyomas, which affected 102 patients (48.1%), 80 of whom were in the PEM group and 22 in the PM group. The second most common accompanying pathology was endometrial polyps (22.2%, n = 47), which was more common among the PM patients (PEM 16.9%, n = 26; PM 36.2%, n = 21). Endometriosis was more prominent in the PEM patients (12.3% n = 19), and 11.6% of the PEM patients had endometrial hyperplasia.

Conclusion: Uterine leiomyoma was the most common gynecological pathology accompanying adenomyosis in both groups, and endometriosis and endometrial hyperplasia were significantly more common in the PEM group compared to the PM group. In line with our results, we think that common etiopathogenic factors may play a role in the pathogenesis of adenomyosis and the concomitant pathologies, and we have discussed our findings here in the light of the literature.

Keywords: Adenomyosis; menopause; myoma; polyp

INTRODUCTION

Adenomyosis, also called myometrial endometriosis, is a nonneoplastic lesion characterized by invasion of the endometrial gland and stromal structures into the myometrium. It is often diagnosed incidentally in hysterectomy specimens. It can be diffuse or focal. It usually presents in the late reproductive period and the clinical findings are nonspecific. It can present with nonpathognomonic symptoms such as abnormal uterine bleeding (AUB), dyspareunia, chronic pelvic pain associated with menstruation, and infertility.

The histopathological diagnostic criteria are the presence of endometrial glands and stroma in the myometrium more than 2.5 mm or at least 25% of the myometrial thickness away from the basal layer of the endometrium (1). The surrounding peripheral myometrial tissue shows varying degrees of hyperplasia and often nodular myometrial smooth muscle proliferation (2). It is possible to observe atrophy, metaplasia, or decidual changes in the endometrial glands as well as endometrial hyperplasia, endometrial intraepithelial neoplasia, and adenocarcinoma development (3). Neoplastic transformation in adenomyosis is quite rare; Koike et al. stated that there are 44 reported cases in the literature (4).

Although the pathophysiology is not entirely understood, there are two suggested mechanisms. The first is invagination of the endometrium into the myometrium and subsequent chronic uterine autotraumatization, tissue damage, and repair mechanisms (5). The second is the Mullerian remnant theory, which argues that adenomyosis develops from implantation of Mullerian duct remnants into the myometrium (6).

The aim of our study was to investigate the gynecological pathologies accompanying adenomyosis in

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Corresponding Author: Eser Colak, Department of Gynecology and Obstetrics, Faculty of Medicine, Konya Medical and Research Center, Baskent University, Konya, Turkey **E-mail:** dresercolak@hotmail.com

perimenopausal (PEM) and postmenopausal (PM) women and to determine their roles in the etiology of adenomyosis. We also evaluated the impact of clinicopathological parameters such as age, contraception methods, gravidity, and parity.

MATERIALS and METHODS

The study protocol was approved after the necessary permissions were obtained from the Başkent University Ethics Committee (register number KA20/286). We complied with the World Medical Association's Declaration of Helsinki regarding ethical conduct in studies involving human subjects. We retrospectively reviewed pathology report archives from between 2008 and 2018 and identified surgical hysterectomy specimens that were histopathologically diagnosed as cases of adenomyosis and recorded accompanying gynecological pathologies (endometriosis, leiomyoma, endometrial hyperplasia, malignancy, etc.). Data regarding medical history were obtained from patient files. In our clinic, menopausal status is defined as "postmenopausal" if the woman reports nospontaneous menstruationinthe previous 12 months and as "perimenopausal" if patientreports irregular spontaneous menstruation, indicating menopause transition. Accordingly, the patients were examined and compared in 2 separate groups: PEM and PM.

The data were evaluated using SPSS version 25 (IBM SPSS Statistics for Windows, Version 25.0, IBM Corp., and Armonk, NY, USA). The variables were expressed as medians (interquartile ranges), percentages, and frequencies. The categorical data were analyzed using Fisher's exact test and chi-square tests. In cases in which the determined frequencies were <20%, the Monte Carlo simulation method was used to include these data in the analysis. Values of $p < 0.05$ and $p < 0.01$ were accepted as the limits for statistical significance.

RESULTS

Adenomyosis was identified in 212 of the 624 hysterectomy specimens that were histopathologically evaluated between 2008 and 2018. Accordingly, the incidence of adenomyosis in our study was calculated as 33.97%. The anamnesis data revealed 154 patients to be premenopausal or PEM and 58 to be PM.

The mean age of the 154 PEM patients was 47.3 years (range: 36-55) and of the 58 PM patients was 58.6 years (range: 43-80).

While 28.8% (n = 61) of the 212 patients diagnosed with adenomyosis had no other concomitant gynecological pathologies, 71.2% (n = 151) had accompanying gynecological pathologies. The most common pathology associated with adenomyosis was uterine leiomyomas (48.1%, n = 102), followed by endometrial polyps (22.2%, n = 47) (Table 1).

Most leiomyomas was ranges of size between 2 and 3 cm of diameter While leiomyomas smaller than 1 cm of diameter usually occur in the PM patients, leiomyomas larger than 5 cm usually occur in the PEM patients. Intramural uterine leiomyoma was the most common type of uterine leiomyoma in both groups. Compare to PM patients majority of leiomyomas was multiple in the PEM patients. Characteristic features of leiomyomas are listed in Table 2.

Table 1. Hysterectomy indications and distribution of pathologies accompanying adenomyosis

		n	%
Group	PEM	154	72.6
	PM	58	27.4
At least one concomitant pathology	No	61	28.8
	Yes	151	71.2
Parity	Multiparous	141	66.5
	Nulliparous	71	33.5
Indication	AUB	136	64.2
	Pelvic pain	34	16
	Prolapse	42	19.8
Leiomyomas	No	110	51.9
	Yes	102	48.1
Endometriosis	No	192	90.6
	Yes	20	9.4
Hyperplasia	No	191	90.1
	Yes	21	9.9
Polyp	No	165	77.8
	Yes	47	22.2

PEM: Pre/perimenopausal, PM: Postmenopausal, AUB: Abnormal uterine bleeding

Table 2. Characteristic features of leiomyomas in premenopausal/ perimenopausal and postmenopausal women patients

			Group	
			PEM (n:80)	PM(n:22)
Size	<1 cm	n	8	8
		%	10.00%	36.37%
	2-3 cm	n	40	12
		%	50.00%	54.55%
	3-4cm	n	15	1
		%	18.75%	4.54%
	>5cm	n	17	1
		%	21.25%	4.54%
Location	intramural	n	73	20
		%	91.25%	90.92%
	submucosal	n	2	1
		%	2.50%	4.54%
	Subserosal	n	5	1
		%	6.25%	4.54%
Focality	One focus	n	23	10
		%	28.25%	45.45%
	Multiple	n	57	12
		%	71.75%	54.55%

The most common complaints in the PEM patients were AUB and pelvic pain, and adenomyosis was frequently diagnosed incidentally in the PM women who underwent hysterectomy due to prolapse (Table 3).

Furthermore, in the PEM group, the prevalence of uterine leiomyoma was 51.9% (n = 80), of endometrial polyps was 16.9% (n = 26), of endometriosis was 12.3% (n = 19), and of endometrial hyperplasiawithout atypia was 11.7% (n = 18). In the PM group, the prevalence of uterine leiomyoma was 37.9% (n = 22), of endometrial polyps was 36.2% (n = 21), and of endometriosis was 1.7% (n = 1) (Table 2).

Comparison of the two groups revealed that 80.1% of the patients with AUB and 91.2% of the patients with pelvic pain were in the PEM group. Meanwhile, 66.7% of the patients who underwent hysterectomy due to prolapse and were incidentally diagnosed with adenomyosis were PM patients (p = 0.001).When compared in terms of concomitant gynecological pathologies, the prevalence of both endometriosis and polyp lesions was significantly different between the two groups (p = 0.018 and p = 0.003, respectively) (Table 4).

Only 3.88% of the patients had a history of using intrauterine devices (IUDs). Two patients (one PEM and one PM) had ovarian granulosa cell tumors. One PEM patient had mucinous adenocarcinoma of the ovary and one PM patient had endometrioid adenocarcinoma.

Table 3. Intragroup distribution of variables

			Group		Total
			PEM	PM	
Parity	Multiparous	n	103_a	38_a	141
		%	66.90%	65.50%	66.50%
	Nulliparous	n	51_a	20_a	71
		%	33.10%	34.50%	33.50%
Indication	AUB	n	109_a	27_b	136
		%	70.80%	46.60%	64.20%
	Pelvic pain	n	31_a	3_b	34
		%	20.10%	5.20%	16.00%
	Prolapse	n	14_a	28_b	42
		%	9.10%	48.30%	19.80%
Leiomyomas	No	n	74_a	36_a	110
		%	48.10%	62.10%	51.90%
	Yes	n	80_a	22_a	102
		%	51.90%	37.90%	48.10%
Endometriosis	No	n	135_a	57_b	192
		%	87.70%	98.30%	90.60%
	Yes	n	19_a	1_b	20
		%	12.30%	1.70%	9.40%
Hyperplasia	No	n	136_a	55_a	191
		%	88.30%	94.80%	90.10%
	Yes	n	18_a	3_a	21
		%	11.70%	5.20%	9.90%
Polyp	No	n	128_a	37_b	165
		%	83.10%	63.80%	77.80%
	Yes	n	26_a	21_b	47
		%	16.90%	36.20%	22.20%
At least one concomitant pathology	No	n	41_a	20_a	61
		%	26.60%	34.50%	28.80%
	Yes	n	113_a	38_a	151
		%	73.40%	65.50%	71.20%
Total		n	154	58	212
		%	100.00%	100.00%	100.00%

PEM: Pre/perimenopausal, PM: Postmenopausal, AUB: Abnormal uterine bleeding

Table 4. Comparison of variables between premenopausal/perimenopausal and postmenopausal women

			Group		Total	p
			PEM	PM		
Parity	Multiparous	n	103$_a$	38$_a$	141	0.851
		%	73.00%	27.00%	100.00%	
	Nulliparous	n	51$_a$	20$_a$	71	
		%	71.80%	28.20%	100.00%	
Indication	AUB	n	109$_a$	27$_b$	136	**0.001****
		%	80.10%	19.90%	100.00%	
	Pelvic pain	n	31$_a$	3$_b$	34	
		%	91.20%	8.80%	100.00%	
	Prolapse	n	14$_a$	28$_b$	42	
		%	33.30%	66.70%	100.00%	
Leiomyomas	No	n	74$_a$	36$_a$	110	0.069
		%	67.30%	32.70%	100.00%	
	Yes	n	80$_a$	22$_a$	102	
		%	78.40%	21.60%	100.00%	
Endometriosis	No	n	135$_a$	57$_b$	192	**0.018***
		%	70.30%	29.70%	100.00%	
	Yes	n	19$_a$	1$_b$	20	
		%	95.00%	5.00%	100.00%	
Hyperplasia	No	n	136$_a$	55$_a$	191	0.157
		%	71.20%	28.80%	100.00%	
	Yes	n	18$_a$	3$_a$	21	
		%	85.70%	14.30%	100.00%	
Polyp	No	n	128$_a$	37$_b$	165	**0.003****
		%	77.60%	22.40%	100.00%	
	Yes	n	26$_a$	21$_b$	47	
		%	55.30%	44.70%	100.00%	
Total		n	154	58	212	
		%	72.60%	27.40%	100.00%	

PEM: Pre/perimenopausal, PM: Postmenopausal, AUB: Abnormal uterine bleeding

DISCUSSION

Adenomyosis is a lesion diagnosed by histological examination of hysterectomy specimens. Therefore, the prevalence of adenomyosis is determined only among hysterectomy specimens, and the actual prevalence is not definitively known.However, it has been shown that adenomyosis can be preoperatively diagnosed using transvaginal ultrasonography (TVUSG) and magnetic resonance imaging (MRI) (7) with high accuracy. In our study, the prevalence of adenomyosis in hysterectomy specimens was 33.97%. The literature reports this rate to be 5-35% for the general population (8). A study that used TVUSG alone determined the prevalence of adenomyosis to be 20.9% (9). However, it was noted that the prevalence reported in that study was lower compared to that in other similar studies.

In our study, 28.8% of the 212 patients had isolated adenomyosis and 71.2% had concomitant gynecological pathologies. Uterine leiomyoma was determined to be the most common pathology accompanying adenomyosis and was found in 51.9% of the PEM cases and 37.9% of the PM cases.Uterine leiomyomas are the most common benign tumors in women of reproductive age. Various studies reported concomitant adenomyosis and uterine leiomyoma in 15-57% of hysterectomy specimens (10). Although the pathophysiology of adenomyosis is not fully understood, authors argue that ectopic endometrial tissue at the endomyometrial border may trigger myometrial hypertrophy and hyperplasia (11).

Wegienka et al. and Leppert et al. suggested that uterine leiomyoma develops as a result of an inappropriate inflammatory response (12,13). The physiological events associated with reproduction, such as ovulation, menstruation, and implantation, can damage the uterus and thus increase the production ofextracellular matrix (ECM) for repair (14). The ECM is involved in the local

production and sequestration of growth factors such as epidermal growth factor (EGF), fibroblast growth factor, and transforming growth factor-beta (TGF-β) and signaling molecules such as amphiregulin. Factors such as TGF-β, platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF) have been shown to be involved in the pathogenesis of leiomyoma (15,16). Sex steroid hormone receptors, inflammatory molecules, extracellular matrix enzymes, and growth factors also play major roles in the pathogenesis of adenomyosis (17).

In our study, we observed that the prevalence of concomitant adenomyosis and uterine leiomyoma was similar between the PEM and PM groups. Wallwiener et al. examined 1955 hysterectomy specimens and observed concomitant adenomyosis and uterine leiomyomasin 398 cases,further stating that 70% of these were PEM patients (18).

Huang et al. emphasized the concomitance of adenomyosis, endometriosis, and uterine leiomyomas and indicated that, among 131 adenomyosis patients, 113 had concomitant endometriosis and uterine leiomyomas, whereas only 18 had uterine leiomyoma concomitance alone (19).

In our study, only 12.3% of the PEM adenomyosis patients and only one PM adenomyosis patient had concomitant endometriosis. Despite having several clinical differences, adenomyosis and endometriosis are thought to develop from a similar pathophysiological basis. Leyendecker et al. emphasized that endometriosis and adenomyosis are mainly associated with tissue damage, excessive physiological repair, and local estrogen production (5). Even though the association between adenomyosis and endometriosis was relatively low in the present study, there are studies that report concomitant endometriosis in up to 70% of adenomyosis cases (20).

Other lesions associated with adenomyosis were endometrial polyps and endometrial hyperplasia (21) and the incidence of concomitant adenomyosis, endometrial polyps, and endometrial hyperplasia is reported to increase with elevated estrogen, early menarche, late menopause, estrogen therapy during menopause, polycystic ovary syndrome, and tamoxifen use (4).This condition is also associated with carcinogenesis and the literature reports the prevalence of adenomyosis in adenocarcinomas to be approximately 16-34% (22-25).

Tetikkurt et al. demonstrated that adenomyosis was accompanied by polyps, hyperplasia, and adenocarcinoma in 40.4% of cases, and they stated that this high rate indicated the significance of hyperestrogenemia in the development of adenomyosis (26). In our study, endometrial hyperplasia without atypia was observed in 11.7% (n = 18) of the PEM cases. However, none of our patients had hyperplasia in adenomyosis foci. Adenomyosis foci are also significant in terms of malignant transformation, albeit rarely. Kucera et al. reported observing malignant transformation in adenomyosis foci in 2.9% of their cases (23), whereas another study reported a similar rate of 2.4% (27).

Studies show that endometrial cancers that develop from adenomyosis foci are commonly low-grade and have a good prognosis. Adenomyosis foci include a hyperplastic and hypertrophic myometrial stroma, creating a mechanical block against invasion. Another associated factor is the increased cytokine secretion in adenomyosis foci [interferon-α (INF-α), INF-gamma, tumor necrosis factor-α (TNF-α), and interleukin-10 (IL-10)], resulting in an increased immune response against the tumor (28-31). However, another hypothesis is that due to direct myometrial stromal invasionadenomyosis can easily invade lymphatic and vascular systems and may be associated with poor prognosis(24).

We evaluated the relationship between ovarian pathologies and adenomyosis and our results indicate that there was no significant correlation between them. In the PEM group, there were 2 mucinous cystadenomas, 1 serous cyst adenoma, 1 granulosa cell tumor, 1 fibroma, and 2 mature cystic teratomas. In the PM group, there were 2 cystadenofibromas,1 mucinous borderline tumor, 3 fibromas, 1 endometrioid adenocarcinoma, and 1 granulosa cell tumor.

It is known that the risk of adenomyosis increases with events that may cause mechanical damage to endometrial tissue, including parity, induced abortion, a high number of cesarean deliveries, andthe use of IUDs (32). There are studies showing that nulliparity is a risk factor for increased blood transfusion requirement in adenomyosis or adenomyosis-related hysterectomies (33). In our study, the parity findings of the two groups were similar, and in both groups the majority of the patients were multiparous. Additionally, 3.88% of the adenomyosis patients had a history of using IUDs.

CONCLUSION

In evaluating our results together with the literature, we drew the following conclusions:

• The most common concomitant gynecological pathology in adenomyosis is uterine leiomyomas in both PEM and PM women, suggesting that this association is not incidental and the etiologies of uterine leiomyomas and adenomyosis may share common grounds.

• In consideration of the possibility of a similar pathogenesis for endometrial polyps, the lower incidence of concomitant endometrial polyps suggests that its pathogenesis may be associated with different mechanisms.

• An independent etiology is supported by the fact that endometrial polyps were more common among PM women.

• The lower mean age in patients with concomitant adenomyosis and endometriosis suggests that this combination leads to severe clinical findings that require hysterectomy at an earlier age.

• The low incidence among PM women may support the involvement of estrogen in its etiopathogenesis.

Competing Interests: The authors declare that they have no competing interest.

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Ethical Approval: The study was approved by the local ethics committee of Baskent University (register number KA20/286). All participants gave written informed consent to participate.

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