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Research Article

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Can We Predict Endometriosis Coexisting with Adenomyosis Based on Clinical Importance?

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Abstract

Objective (s): The aim of this analysis was to determine the characteristics of concomitant endometriosis and adenomyosis in women who underwent a hysterectomy for benign uterine diseases.

Materials and Methods: We conducted a retrospective study of women undergoing hysterectomy with a histologic diagnosis of both adenomyosis and endometriosis and with adenomyosis but no endometriosis. The study examined 322 patients, 162 women with both adenomyosis and endometriosis and 160 women with only adenomyosis. The two groups were compared with respect to sociodemographic, clinical, and histopathological characteristics.

Results: Results of multivariate logistic regression analyses showed that women with both adenomyosis and endometriosis had a higher primigravida (odds ratio [OR], 0.093; 95% confidence interval [CI], 0.038-0.228), and higher Ca 125 levels (OR, 0.380; 95% CI, 0.183–0.790), more frequent pelvic pain (OR, 0.250; 95% CI; OR 0.380, 95% CI, 0.183–0.790), and more frequent dysmenorrhea (OR, 1.234; 95% CI; OR 0.978–1.678) compared with women with adenomyosis only.

Conclusions: Preoperative elevations in Ca 125 levels, dysmenorrhea, and pelvic pain may be useful clinical predictors for concomitant adenomyosis and endometriosis.

Keywords: *Adenomyosis; Endometriosis; Hysterectomy*

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Introduction

Endometriosis and adenomyosis are common benign gynecologic conditions and may occur together. Endometriosis and adenomyosis are poorly understood disorders that affect women of reproductive age, causing pelvic pain, dysmenorrhea, and infertility. Adenomyosis is defined as the presence of endometrial glands and stroma within the myometrium, whereas endometriosis is the presence of endometrial tissue outside the uterus [1].

Endometriosis affects 10% of women during their reproductive years. Endometriosis is seen at the time of laparoscopy in 70% of women examined for chronic pelvic pain and infertility [2]. Adenomyosis is a difficult diagnosis, often established only during a

pathological examination of the hysterectomy specimen. Concurrent endometriosis was observed in 9% to 10% of patients with adenomyosis [3,4]. This study evaluated the clinical importance associated with a surgically confirmed diagnosis of endometriosis with coexistent adenomyosis.

Materials and Methods

The study included 322 patients who underwent hysterectomy and had confirmed pathology for adenomyosis. This retrospective study was based on the medical records of patients who were operated at Zekai Tahir Burak Research Hospital, Ankara, Turkey between March 2012 and September 2016. Approval was obtained from the local ethics committee (no:27.01.2016/14).

The study included 162 women with both adenomyosis and endometriosis, and 160 women with only adenomyosis. The two groups were compared with respect to sociodemographic, clinical, and histopathological characteristics including age, gravidity, parity, history of abortion, menopause, preoperative Ca 125 levels, depth and severity of adenomyosis (focal or dıffuse), uterine volume, myometrial thickness, corpus-fundus diameter, and hemoglobin levels. Clinical symptoms were inspected as pelvic pain, dysmenorrhea, dyspareunia, and abnormal uterine bleeding.

The presence of adenomyosis and endometriosis was established by the confirmation of histopathologic examination. Patients with inadequate medical records were excluded from the study. Statistical analyses were performed using SPSS for Windows (SPSS, Inc., Chicago, IL, USA). A Student's t-test was used for the comparison of normally distributed data while a Fisher's exact test was performed for categorical data. Results of multivariate logistic regression analyses were used to determine the role of clinical factors to predict the coexistence of adenomyosis and endometriosis. All statistical tests conducted were two-tailed and a probability value less than .05 was considered significant.

Results

The mean age was higher in the adenomyosis only group compared with the concomitant adenomyosis and endometriosis group (52.19 ± 6.61 vs 47, 74 ± 4.68, p = .001). The mean gravidity (4 (0–13) vs 2 (0–10) p = .001), parity (3 (0–12) vs 2 (0–6) p = .001), and abortion (p = .001) were higher in the adenomyosis only group compared with the concomitant adenomyosis and endometriosis group. Preoperative hemoglobin was lower in the concomitant adenomyosis and endometriosis group compared with the only adenomyosis group (p = .001). We further evaluated whether there was any association between Ca 125 levels. Preoperative Ca 125 levels were higher in the concomitant adenomyosis and endometriosis group compared with the only adenomyosis group (p = .001). Patients with concomitant adenomyosis and endometriosis tended to be postmenopausal, and this tendency was statistically significant (p = .001).

There was no statistically significant difference between uterine volume, myometrial thickness, and corpus-fundus diameter. Histopathological evaluation of surgical specimens demonstrated that diffuse adenomyosis was higher than diffuse adenomyosis in both groups. The presence of dıffuse adenomyosis was significantly more frequent in concomitant adenomyosis and endometriosis group (p = .001). Likewise, histopathological examinations of the uterus regarding endometrial pathologies were performed. Coexistence of endometrial hyperplasia was more frequent in the only adenomyosis group (p = .01) when compared with that in the adenomyosis and endometriosis group.

Only one patient had a diagnosis of malignancy in the concomitant adenomyosis and endometriosis group. Symptoms of the groups included in our study are presented in Table 2. Pelvic pain and dysmenorrhea occurred more frequently in the adenomyosis and endometriosis group when compared with the group with only adenomyosis, and this was statistically significant (p = .047 and p = .036, respectively). The other pain symptom included in this study was dyspareunia and there was no significant difference between the two groups with regard to this symptom. We evaluated uterine bleeding abnormalities including menorrhagia only and both metrorrhagia and postmenopausal bleeding, and there was no significant difference between the two groups regarding abnormal bleeding.

Variables	Adenomyosis (n = 160)	Endometriosis with Adenomyosis (n = 162)	P
Age(years) mean ± SD	52.19 ± 6.61	47,74 ± 4.68	.001*
Median gravidity (min-max)	4 (0–13)	2 (0–10)	.001*
Parity	3 (0–12)	2 (0–6)	.001*
History of abortion	88	62	.001*
Menopause	89 (54.6%)	21 (13%)	.001*
Adenomyosis			.02
Focal	63 (39.37%)	38 (23.5%)	
Diffuse	97 (60.62%)	124 (76.5%)	
Ca-125 (U/ml)	27.24 ± 57.06	57.05 ± 89.76	.001*
Uterine Volume (cm3)	1867.87 ± 1804.63	2316.48 ± 2729.89	.08
Myometrial thickness (cm)	9.95 ± 1.06 (8–11)	10.1 ± 0.98 (8.5–11)	.908
Corpus-fundus diameter (cm)	2.21 ± 0.66 (1.2–3)	2.24 ± 0.51	.708
Hb (mg/dl)	12.2 ± 1.74	11.43 ± 1.86	.001*

*P < 0.05, statistically significant. Hb: Hemoglobin.

Table 1: *Patient Demographics and Clinical Characteristics.*

Symptoms	Adenomyosis	Endometriosis with Adenomyosis	P
Pelvic pain	81 (51%)	64 (39.5%)	0.047*
Abnormal uterine bleeding	56 (35%)	55 (33.9%)	0.208
Dysmenorrhea	16 (10%)	22 (13.5%)	0.036
Dyspareunia	6 (4%)	21 (13.1%)	0,627*

*P < 0.05, statistically significant.

Table 2: *Clinical Symptoms.*

	Adenomyosis	Endometriosis with Adenomyosis	P
Endometrial pathology			.001*
Hyperplasia	39(27%)	9(5%)	
Malignancy	0(0%)	1(6%)	

*P < 0.05, statistically significant.

Table 3: *Concomitant Gynecological Pathology.*

	Wald	SE	OR	95% CI	P
> 50 years old	0.742	0.354	0.738	0.369–1.475	.389
Primipara	27.223	0.454	0.093	0.038–0.228	<.001*
Multipara	1.746	0.684	2.470	0.646–9.443	.186
Abortion	0.147	0.128	1.05	0.818–1.349	.702
Diffuse adenomyosis	11.66	0.33	0.320	0.167–0.616	.001*
Ca 125 > 35	6.71	0.373	0.380	0.183–0.790	.010*
Uterine volume > 1000	0.091	0.340	0.903	0.464–1.757	.763
Hb < 11	1.818	0.333	0.638	0.332–1.226	.178
Menopause	19.792	0.407	6.125	2.756–13.610	< .001*
Pelvic pain	3.936	0.700	0.250	0.63–0.983	.047*
Abnormal uterine bleeding	1.584	0.708	0.410	0.102–1.643	.208
Dysmenorrhea	2.314	0.546	1.234	0.978–1.678	.036*
Dyspareunia	0.236	0.804	0.677	0.140–3.270	.627

*P < 0.05, statistically significant.

Table 4: *Results of Multivariate Logistic Regression Analyses.*

Multiple regression analysis of clinical factors foreseeing the association of adenomyosis and endometriosis

Discussion

The objective of this study was to determine the characteristic symptoms and findings of co-occurring adenomyosis with endometriosis and adenomyosis only to both facilitate the detection of co-occurrence and improve treatment modalities.

As recommended by the ESHRE (European Society of Human Reproduction and Embryology) guidelines, the gold diagnostic standard for endometriosis is the combination of laparoscopy visualization and histologic confirmation of the presence of endometrial glands and/or stroma, although adenomyosis requires hysterectomy followed by histopathologic confirmation [5].

It was thought that both endometriosis and adenomyosis affected reproductive-age women who had cyclic bleeding. Because of its invasiveness and the need for hysterectomy, intervention for adenomyosis tends to be after menopause when compared with endometriosis [5]. Adenomyosis is regarded as a disease of multiparous and older women [6]. Some contingent mechanisms were proposed regarding the correlation between parity and adenomyosis pathology. First, pregnancy may facilitate the formation of adenomyosis by invasion of trophoblasts into myometrial fibers. Second, seeding of endometrial tissue by Cesarean section may be a causative factor of iatrogenic adenomyosis. Third, hormonal alterations of pregnancy may lead to the development of ectopic endometrium [7].

Multiple factors that encourage the formation of adenomyosis have been described by recent studies. Having more than one pregnancy, invasive surgeries, and estrogen treatment seem to correlate with adenomyosis [7]. In agreement with previous studies, we found that a high percentage of women with adenomyosis were multiparous although multipara was higher in the concomitant adenomyosis and endometriosis group [7]. This observation may be because patients who have severe endometriosis frequently have endometriosis-associated infertility as a consequence of both anatomical and immunological changes [7]. As a result of infertility treatments, diagnosing nulliparous women with endometriosis might become more frequent.

Although pelvic pain, dysmenorrhea, uterine tenderness, and abnormal bleeding were known as suggestive symptoms of adenomyosis, they can be thought undoubtedly as the symptoms of endometriosis and uterine fibroids. [6] In a recent study named ‘‘Study of

Women's Health Across The Nation,'' investigators presented possible specific symptoms for adenomyosis. It was determined to have a similar frequency of symptoms in both the absence and presence of adenomyosis in patients who had a hysterectomy for fibroids, endometriosis, and abnormal bleeding patterns [8]. According to the results of our study, we found that patients who had adenomyosis accompanied by endometriosis were more likely to experience both pelvic pain and dysmenorrhea but no significant difference between bleeding patterns.

There is a distinct correlation between leiomyoma uteri, endometrial hyperplasia, adenomyosis, and endometriosis as these conditions are hormonally driven [9,10]. Several studies have demonstrated the hormonal basis and co-occurrence of these disorders [11]. It is also speculated that there is a clear association between adenomyosis and particularly deep infiltrative endometriosis. The prevalence of endometriosis in women with adenomyosis seems higher than in patients with only leiomyoma uteri [12].

Several authors have described different symptoms related to the co-occurrence of adenomyosis and endometriosis [13] and pointed at a strong association between the two occurrences [13,14,] Kissler., *et al*. emphasized the high frequency of the coexistence of adenomyosis with severe and prolonged dysmenorrhea in patients with endometriosis [15] Larsen., *et al*. and Gonzalez., *et al*. described the correlation between the severity of endometriosis and poorness of prognosis with the degree of adenomyosis [16,17] Di Donato evaluated characteristic points related to adenomyosis in patients undergoing surgery for endometriosis. In this study, a particular endometrial shape that is based on the pelvis' posterior compartment, was identified and named the "question mark sign." It is associated with adenomyosis and strongly related to the presence of posterior deep infiltrating endometriosis [7,18].

In disagreement with recent studies, two different studies from Milan reported that the concomitant diagnosis of endometriosis was found in 9%–10% of patients with adenomyosis. In contrast, 40.4% of the patients with adenomyosis were found to have endometriosis also. The co-occurrence of adenomyosis and endometriosis in these two studies from Milan was not significant [19,20].

Bergholt., *et al*. described an association between endometrial hyperplasia and adenomyosis [21]. Although it is well defined that there is an overlap in their pathologic development, we could not find a significant relation between adenomyosis with either the presence or the absence of endometriosis and endometrial hyperplasia supporting the study of Genc., *et al*. [22]

Adenomyosis is not typically suspected before performing hysterectomy [6] İmaging techniques can be used for the diagnosis. An ultrasonographic diagnosis depends on the experience of the sonographer otherwise magnetic resonance is not cost effective for routine examinations [6]. Although the incidence of adenomyosis seems distinct in different studies, the prevalence of adenomyosis is higher in patients with endometriosis compared with healthy women [23]. It is fortuitous to observe co-occurrence to design a clinical approach.

In our study, patients with endometriosis and adenomyosis complained of more severe pain symptoms (dysmenorrhea, pelvic pain) compared with the other group. It is similar to the results of the study by Di Donato [7]. Distinctively dyspareunia presented no significant difference between the two groups. Although Gonzales., *et al*. have described a strong correlation between adenomyosis and particularly endometriosis of the rectosigmoid [7], which might culminate with dyspareunia.

We thought that our results could be the cause of different types of endometriosis, with regard to both the intensity and the depth of lesions included in this study. Endometriosis is often called the chameleon of the pelvis because of its multifaceted behavior. It is usually possible to miss endometriosis by laparotomy because of the restriction to visualize the posterior cul-de-sac, ovarian fossa, and broad ligaments details [11]. In our study, detailed visual inspection was performed, all possible lesions were biopsied, and histopathologically proven disease was included in the study.

It is possible that endometriosis of other pelvic organs was missed in the group, which was described as adenomyosis only and this may be considered as an alternative explanation. Abnormal bleeding is thought to be related to the depth of penetration of adenomyotic glands into the myometrium and to the frequency of deep endometrial glands within the myometrium [7]. We observed no significant difference between bleeding patterns of the two groups.

Ca 125 levels are the most important marker for detecting and following the response to the treatment of endometriosis [24]. This marker can also be used for the differential diagnosis of adenomyosis and leiomyoma uteri. Although Ca 125 levels tend to be higher in severe adenomyosis, we could not find a comparison for the levels in both adenomyosis and endometriosis in recent studies [25,26]. According to our results, adenomyosis with concomitant endometriosis has higher levels of Ca 125 when compared with adenomyosis only.

Dysmenorrhea and pelvic pain following optimal endometriosis surgery might be signs of concomitant adenomyosis [6]. These symptoms might lead the clinician to the treatment of adenomyosis. İn recent studies several medical and surgical treatment choices were ınvestigated. Uterine artery embolization, levonorgestrel-releasing ıntrauterine systems, and antiangiogenic agents like cabergoline can be used as alternatives to surgery [6]. If we consider an opposite case; it can be helpful to evaluate whether a patient has only adenomyosis or adenomyosis with endometriosis to map out the medical treatment to slow down the progression of endometriosis after hysterectomy for adenomyosis.

It may be useful to know co-occurrences to heal clinical symptoms after surgery. We aimed to find specific markers and symptoms for the co-occurrence of adenomyosis with endometriosis in this study. In light of the findings of our study, it might be useful to evaluate patients who had a diagnosis of adenomyosis with dysmenorrhea, pelvic pain, and high preoperative Ca 125 levels for concurrent endometriosis. Diagnosis and treatment of both etiologies may potentially lead to lower treatment failures, decreased recurrence rates, and higher symptomatic improvement.

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