# Coexistence of gynecological pathology with endometriosis and adenomyosis

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**Abstract.** Both endometriosis and adenomyosis can impact quality of life. Endometriosis is a chronic, benign, condition characterized by the growth of endometrium outside the uterus, which affects ~10% of women from menarche to menopause, globally. Adenomyosis is a benign gynecological condition, which is defined as the infiltration of ectopic endometrial tissue within the underlying myometrium. It is often diagnosed in perimenopausal women aged 40-50 years, with a prevalence that varies widely (ranging from 1-70%). The aim of the present study was to determine the histological coexistence of gynecological pathology in women with endometriosis, adenomyosis and those with both. In the present retrospective study, data retrieved from the medical records of women that underwent abdominal hysterectomy with bilateral or unilateral salpingo-oophorectomy at the Department of Obstetrics and Gynecology of Venizeleio General Hospital and the Third Department of Obstetrics and Gynecology of Aristotle University of Thessaloniki (Greece) between 2000-2022 were included. Patients were divided into three groups; group 1 included those with endometriosis, group 2 included those with adenomyosis and group 3 included those with both endometriosis and adenomyosis. Cases with inadequate medical records and those lacking histological diagnoses were excluded. The total number of patients included in the present study was 1,692 women; group 1 included 495 (29.2%) patients, group 2 included 1,096 (64.8%) patients and group 3 included 101 (6.0%) patients. The results of the present study revealed that the most common pathology was leiomyomas (43.3%), followed by endometrial and cervical polyps (17.6 and 9.8%, respectively). Benign ovarian (12.2%) and paraovarian cysts (13.7%) were also observed. Compared with groups 1 and 2, leiomyomas were significantly more common in group 3 (67.3%). Endometrial cancer was significantly more common in group 2 (9.3%), compared with group 1 (1.6%) and group 3 (4%). The present study suggested that endometriosis, adenomyosis or the concomitant presence of both may coexist with various benign and malignant gynecological diseases.

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## Introduction

Endometriosis is a chronic benign systemic proinflammatory condition, which is characterized by the growth of endometrium (glands and stroma) outside the uterus, mostly in the ovaries, followed by the soft tissue, gastrointestinal and urinary tract. Globally, it affects 7-10% of women with an incidence of 38% in infertile women and 71-87% in women with chronic pelvic pain (1,2). Histologically endometriosis is classified as having a typical and atypical form. Atypical endometriosis indicates a premalignant lesion and is characterized by areas of marked cellular atypia with morphologic features similar to those of clear cell carcinoma. By contrast, typical endometriosis is a benign condition that involves endometrial-like tissue growing outside the uterus (3,4).

Adenomyosis is a benign uterine condition, which is characterized by the infiltration of ectopic endometrial tissue (glands and stroma) within the underlying myometrium (5,6). Depending on the distribution within the myometrium, adenomyoma can be classified as focal, diffuse or polypoid adenomyoma (5,6). Adenomyosis appears in late childbearing years (40-50 years of age). It is accompanied by menorrhagia in 40-50% of cases, by dysmenorrhoea that does not respond to the standard anti-inflammatory treatment (such as non-steroidal anti-inflammatory drugs) in 15-78% of cases and infertility in 11-12% of cases. The global prevalence of adenomyosis among patients after a hysterectomy varies from 5-70% (5,6). However, European estimates using imaging (such as ultrasound and MRI) suggest a prevalence of 20-35%, but the data are limited (6). In 1927, the study by Sampson (7) coined the term endometriosis. Furthermore, in 1972, a study by Bird (8) defined adenomyosis as the benign invasion

of endometrium into the myometrium, surrounded by the hypertrophic and hyperplastic myometrial tissue. Although, adenomyosis was previously called 'endometriosis interna', a form of endometriosis, it is well documented that both diseases are distinct. Endometriosis is considered to form from the functional endometrium and adenomyosis is considered to form from the basal endometrium. Various etiological factors, such as genetic, endocrine, autoimmune, environmental and anatomical factors, serve a role in the development of both entities (1,2,6-9). It is hypothesized that retrograde menstruation is the primary mechanism for endometriosis and that local invasion, cellular proliferation and angiogenesis are mechanisms for adenomyosis (1,2,6,7,9). Furthermore, patients with breast cancer that are treated with tamoxifen are at a distinct risk of endometriosis, adenomyosis and several other gynecological conditions such as endometrial polyps, hyperplasia and uterine cancer (10).

Gynecological diseases such as adenomyosis, leiomyomas, endometriosis, endometrial polyps, hyperplasia, endometrial and ovarian cancer often coexist, which suggests that they may share common pathogenic mechanisms such as the presence of hyperestrogenism, inflammatory, environmental and genetic altered features (1,5,11,12).

The aim of the present study was to determine the histological frequency of various benign and malignant gynecological diseases among women with endometriosis, adenomyosis or both that underwent gynecological surgery.

## Materials and methods

*Patients*. Women (aged ≥18 years) that underwent abdominal hysterectomy with bilateral or unilateral salpingo-oophorectomy with a clear medical record documentation, at the Department of Obstetrics and Gynecology of Venizeleio General Hospital (Heraklion, Greece) in January 2000 to December 2022 and the Third Department of Obstetrics and Gynecology of Aristotle University of Thessaloniki (Thessaloniki, Greece) in January 2009 to December 2019, were included in the present study. Data were collected retrospectively and included the indication for gynecological operation, age, clinical and histopathological findings.

Patients were divided into three groups, namely group 1 (which included women with endometriosis), 2 (which included women with adenomyosis) and 3 (which included patients with both endometriosis and adenomyosis). All data were retrieved from the medical records. Cases with inadequate medical records and those lacking histological diagnoses were excluded. Patient consent for participation was waived by the ethics committees due to the retrospective nature of the present study. The Ethics Committees of Venizeleio General Hospital (approval no. 124-17-18/12/2019; Heraklion, Greece) and Aristotle University of Thessaloniki (approval no. 1130-03/07/2020; Thessaloniki, Greece) both approved the protocol of the present study.

*Statistical analysis*. The descriptive statistics are presented as mean ± standard deviations or as frequencies and percentages. Associations between categorical variables was estimated using the Chi-square test of independence. The parameter 'age' was analyzed using one-way ANOVA followed by Tukey's post hoc test. Multinomial logistic regression was carried out to detect factors associated with pathology. Statistical analysis was carried out using IBM SPSS Statistics (version 25.0; IBM Corp.).

## Results

*Eligible population*. In total, 3,511 women underwent abdominal hysterectomy with bilateral or unilateral salpingo-oophorectomy at the Department of Obstetrics and Gynecology of Venizeleio General Hospital (Heraklion, Greece) and the Third Department of Obstetrics and Gynecology of Aristotle University of Thessaloniki (Thessaloniki, Greece) in the study period. However, of these 3,511 women, only 1,692 cases were eligible for inclusion in the present study, having endometriosis, adenomyosis or both conditions. The majority of cases had adenomyosis (n=1,096; 64.8%; group 2), followed by endometriosis (n=495; 29.3%; group 1), while 101 cases had both endometriosis and adenomyosis (6.0%; group 3). The mean age of the total study population was 50.16±12.74 years (range, 16-85 years). However, the mean age of patients with adenomyosis was significantly higher (55.34±10.21) compared with those of the other two groups.

*Reported pathologies among the groups*. In the total sample of 1,692 women, the most commonly noted pathology was leiomyomas (43.3%), followed by endometrial polyps (17.6%). Benign ovarian (12.2%) and paraovarian cysts (13.7%), and cervical polyps (9.8%) were also frequently observed. The occurrence of leiomyomas was significantly more frequent in patients in group 3 (67.3%) compared with those in groups 1 (24.2%) or 2 (49.6%). A similar result was observed for the frequency of ovarian cysts, which were more common in the patients in group 3 compared with those in groups 1 or 2 (Table I).

Among gynecological malignancies, endometrial cancer was significantly more frequent in patients in group 2 (9.3%), compared with those in groups 1 (1.6%) or 3 (4.0%) (Table I). However, further analysis with multinomial logistic regression did not identify adenomyosis as a factor associated with endometrial cancer (P=0.426).

## Discussion

The present study demonstrated that both endometriosis and adenomyosis can co-exist with various benign, premalignant or malignant gynecological diseases such as leiomyomas, endometrial and cervical polyps, and benign ovarian and paraovarian cysts. Regarding gynecological malignancy, adenomyosis was more commonly associated with endometrial cancer compared with cervical or ovarian cancer.

Uterine fibroids are mainly detected in women aged 30-50 years old and are due to the effects of estrogen and progesterone levels and their metabolism. Under *in vitro* and *in vivo* conditions, uterine fibroids and endometriotic ectopic cells express aromatase, resulting in increased concentrations of estrogen in the tissues (13). It is considered that an enlarged fibroid mass can change the shape, size and location of the uterus within the pelvic cavity and that this may result in retrograde menstruation and endometriosis (14,15). Our previous study confirms that fibroids coexist commonly with endometriosis in perimenopausal women, whereas adenomyosis is more

Table I. Frequencies of various pathologies among the patients.

| Characteristic | Patients with endometriosis (n=495) | Patients with adenomyosis (n=1,096) | Patients with endometriosis and adenomyosis (n=101) | P-value |
|---|---|---|---|---|
| Age, years (mean ± SD) | 38.63±10.78 | 55.34±10.21 | 50.48±8.70 | <0.001 |
| Cervical polyps, N (%) | 19 (3.8) | 130 (11.9) | 17 (16.8) | <0.001 |
| Endometrial polyps, N (%) | 24 (4.8) | 261 (23.8) | 13 (12.9) | <0.001 |
| Endometrial hyperplasia without atypia, N (%) | 6 (1.2) | 72 (6.6) | 4 (4.0) | <0.001 |
| Endometrial hyperplasia with atypia, N (%) | 2 (0.4) | 39 (3.6) | 1 (1.0) | 0.001 |
| Leiomyomas, N (%) | 120 (24.2) | 544 (49.6) | 68 (67.3) | <0.001 |
| Benign ovarian cysts, N (%) | 36 (7.3) | 153 (14.0) | 17 (16.8) | <0.001 |
| Paraovarian cysts, N (%) | 41 (8.3) | 169 (15.4) | 22 (21.8) | <0.001 |
| Cervical cancer, N (%) | 11 (2.2) | 43 (3.9) | 0 (0.0) | 0.034 |
| Endometrial cancer, N (%) | 8 (1.6) | 102 (9.3) | 4 (4.0) | <0.001 |
| Ovarian cancer, N (%) | 1 (0.2) | 19 (1.7) | 0 (0.0) | 0.017 |

In the same specimen, endometriosis or adenomyosis can co-exist with more than one gynecological condition.

prominent in postmenopausal women (16). In patients with leiomyomas, the reported prevalence of adenomyosis varies from 15-60% in women undergoing hysterectomy or another gynecological operation. Furthermore, 70% of women in the general population will acquire leiomyomas at any given point during their reproductive years, the majority of which occur between the ages of 30-50 years (6,17). In the present study, it was confirmed that cases of leiomyomas are more common in patients with endometriosis and adenomyosis compared with patients with endometriosis or adenomyosis.

According to the literature, endometrial hyperplasia and polyps are mostly observed during reproductive years and in perimenopause and result from hormonal alternations, overexpression of aromatase, inflammation, gene mutations and monoclonal cell hyperplasia (18,19). Women with a diagnosis of pre-existing endometriosis (of at least 12 months), with no other diagnosed pathology, were studied in a large population-based observational study. The possible occurrence of endometrial cancer or hyperplasia was studied with a mean follow-up of 6.4 years. Women with endometriosis were at greater risk of developing endometrial hyperplasia (1.85 times) and endometrial cancer (1.35 times) compared with women without endometriosis (20). Regarding polyps, a study by McBean *et al* (21) was the first to identify an association between endometriosis and polyps. A study by Huang and Xiang (22) suggests that endometrial polyps may be due to reactive endometrial hyperplasia due to long-term repetitive mechanical stimulation and the presence of biological inflammatory factors, such as VEGF and TGFβ. In a study by Zhang *et al* (23), it is hypothesized that endometrial inflammation indicates the common mechanism leading to the coexistence of endometriosis with endometrial polyps. Additionally, in the aforementioned meta-analysis it is observed that the risk of coexistence is prominent in stages 2-4 of endometriosis. However, a study by Zheng *et al* (24) considers that the frequency of coexistence does not differ notably according to the stage of endometriosis. Endometrial polyps were found in 46.7% of cases with endometriosis and in 16.5% of the control group (24). The study by Kim *et al* (25), due to a high risk of co-occurrence, recommends hysteroscopy in infertile women with endometriosis, even if medical imaging is not suggestive of endometrial polyps.

In terms of adenomyosis, a retrospective study by Dayal and Nagrath (26), using 353 adenomyosis histological confirmed specimens, demonstrates the co-existence of endometrial hyperplasia in 12.46% and uterine polyps in 7.64% of cases. Additionally, a study by Tetikkurt *et al* (27) confirmed 71 cases with endometrial polyps, 9 cases with hyperplasia and concurrent presence of endometrial polyps and hyperplasia in 6 women out of a total of 319 cases with a histopathological diagnosis of adenomyosis. However, a study by Bergholt *et al* (28) observes that the presence of endometrial hyperplasia at the time of operation is the only variable associated with adenomyosis, as was also demonstrated in the present study. In a study by Baskin *et al*, six adult female monkeys are ovariectomized and receive subcutaneous implants containing 200 mg estradiol. The subsequent necropsy reveals the coexistence of endometrial hyperplasia, polyps or adenomyosis; thus, hyperestrogenism may result in various gynecological conditions (29). In the present study, endometrial and cervical polyps were significantly detected in the patients with adenomyosis and the patients with both endometriosis and adenomyosis, respectively.

With regards to benign ovarian growth, endometriosis can coexist with various benign and premalignant ovarian masses such as serous/mucinous cystadenomas, borderline ovarian tumors and teratomas (11,30). A retrospective study by Oral *et al* (31), using 530 cases with ovarian cancer and 131 women with borderline ovarian cancer, reveals that concomitant endometriosis occurs in 7.3% of cases. However, our previous study recently concludes that further research is required to investigate the pathway through which ovarian teratomas are negatively associated with the risk of developing endometriosis (32). A previous case series study by Vercellini *et al* (33) confirms the coexistence of adenomyosis and ovarian cysts in 21.4% of cases. Moreover, a previous prospective

cross-sectional study, out of 100 hysterectomy cases, reveals the coexistence of adenomyosis with non-cancerous ovarian cyst in 25% of cases (34). Our previous study retrospectively investigates the medical records of 647 patients with adenomyosis in order to examine a possible association between adenomyosis and benign, premalignant and malignant gynecological diseases in women who underwent gynecological surgery. The aforementioned study demonstrates that adenomyosis co-exists with various gynecological conditions, such as leiomyomas and endometrial polyps, but it did not report a prominent association of adenomyosis with other gynecological pathologies compared with the general population (17). However, a paraovarian or paratubal cyst (POC), a mass located in the broad ligament or the mesosalpinx, has a high prevalence (5-20%) amongst the adnexal masses. In the present study, benign ovarian cysts and POC were prominent in group 3, followed by group 2. Due to hormonal alternations, they are mainly found during reproductive age; thus, they can coexist with endometriosis or adenomyosis (11,35). POC can result in disturbed tubal mobility, a condition that may result in the presence of endometriosis (36,37).

The present study found 101 cases with concurrent endometriosis and adenomyosis. In 2018, a retrospective study, including 1,000 cases with a histological confirmation of endometriosis, concludes that women with endometriosis should receive counseling regarding the risk of accompanying adenomyosis (11). Moreover, in 2019, our previous study retrospectively demonstrated the coexistence of adenomyosis with endometriosis in 16% of women in perimenopause and in 32.6% of women in postmenopause (16).

Although rarely, both endometriosis and adenomyosis may exhibit cancerous behavior or coexist with gynecological malignancy. Prolonged exposure to estrogens, genetic defects, environmental factors, immune dysregulation and oxidative stress are possible pathogenic mechanisms (38-41). Sampson's criteria are used for both adenomyosis and endometriosis malignant transformation (42,43). Neoplasms that develop from endometrial ectopic implants in endometriosis are divided into two categories; ovarian, which accounts for 75% of the cases described in the literature and extra ovarian such as endometrial, cervical and breast cancer (41). Cases of ovarian cancer due to endometriosis have unique features, such as endometrioid carcinoma or clear cell carcinoma, the diagnosis is usually made earlier compared with other types of ovarian cancer and the prognosis is better (44,45). Although malignant transformation may occur in 1% of cases with ovarian endometriosis, there is a strong link between endometriosis and ovarian cancer. In particular, women with endometriosis have a 4.2-fold higher risk of ovarian cancer compared with the general population. Therefore, it is recommended to create screening and prevention programs for this population in the future (46-48). The study by Saavalainen *et al* (49) concludes that the type of endometriosis a woman has may determine the risk of gynecological cancer. The risk of ovarian cancer was highest among women with ovarian endometriosis but low among cases with peritoneal and deep infiltrating endometriosis (49). Previously, a large retrospective study reports that endometrial cancer with concomitant endometriosis is highly associated with ovarian endometrioid carcinoma (50). Furthermore, epidemiological data show that the risk of developing endometrioid carcinoma of the endometrium doubles or even triples in cases with endometriosis (51,52). However, a study by Poole *et al* (53) demonstrates that there is not a strong association between endometriosis and endometrial cancer, and this indicates that both conditions follow a different molecular pathogenesis. Our previous study retrospectively confirms that women with cervical endometriosis are at greater risk of developing ovarian, endometrial and cervical cancer compared with women without endometriosis (54). Another large population-based historical cohort study confirms that, compared with cases not acquiring the conditions, patients with adenomyosis are at higher risk of endometrial and thyroid cancer, while women with endometriosis are at greater risk of endometrial and ovarian cancer (55).

However, a large pilot study did not reveal a notable difference in terms of epidemiologic, clinicopathologic and prognostic characteristics in patients with endometrial cancer and adenomyosis compared with patients with only endometrial cancer (56). In addition, a systematic review and meta-analysis by Raffone *et al* concludes that the pathology of adenomyosis and endometrial cancer are two unassociated entities (57). Recently, for the first time, a large retrospective study by Yang *et al* (58) describes a possible protective mechanism of adenomyosis against cervical cancer invasion, a phenomenon that is also previously discussed in a study by Machida *et al* (39) for endometrial cancer. The findings of the present study indicated endometrial cancer in patients with adenomyosis; however, further analysis, with multinomial logistic regression, did not identify adenomyosis as a factor associated with endometrial cancer.

The present study had a number of limitations. Firstly, there was a lack of long-term follow-up data, which meant that distinguishing cases with concurrent gynecological malignancy or malignant transformation of adenomyosis and/or endometriosis was limited. Moreover, the retrospective aspect of the present study was a limitation. However, strengths of the present study include the histological confirmation of all cases and the large number of patients that were included in the present study.

In conclusion, the present study demonstrated that endometriosis, adenomyosis or the concomitant presence of both conditions may coexist with various benign and malignant gynecological diseases. Furthermore, patients with adenomyosis may be associated with endometrial cancer. However, additional longitudinal studies are required in order to generalize the findings of the present study in other populations.

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**Availability of data and materials**

The data generated in the present study may be requested from the corresponding author.

## Authors' contributions

MM, IK and CM conceived and designed the present study and drafted the manuscript. MM, CM, IK and IT obtained the data. MM, KK, CM, TD, AM, DAS and IK analyzed and interpreted the data. DAS, KK, TD, AM and IT searched the literature for related studies to be included in the manuscript. IK, DAS, AM, TD, KK and IT critically revised the manuscript. All authors read and approved the final version of the manuscript. MM and IK confirm the authenticity of all the raw data.

## Ethics approval and consent to participate

The Ethics Committees of Venizeleio General Hospital (approval no. 124-17-18/12/2019; Heraklion, Greece) and Aristotle University of Thessaloniki (approval no. 1130-03/07/2020; Thessaloniki, Greece) approved the protocol of the present study.

## Patient consent for publication

Not applicable.

## Competing interests

MM, IT, CM, KK, TD, AM and IK declare that they have no competing interests. DS is the Managing Editor of the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article.

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