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Co-existence of benign gynecological tumors with endometriosis in a group of 1,000 women

CHAROULA MATALLIOTAKI[1], MICHAIL MATALLIOTAKIS[1], PANAGIOTIS IEROMONACHOU[2], GEORGE N. GOULIELMOS[3], MARIA I. ZERVOU[3], AGGELOS LALIOTIS[4], DEMETRIOS A. SPANDIDOS[5], AYDIN ARICI[6] and IOANNIS MATALLIOTAKIS[1]

Departments of [1]Obstetrics and Gynecology, and [2]Histopathology, Venizeleio General Hospital, 71409 Heraklion; [3]Section of Molecular Pathology and Human Genetics, Department of Internal Medicine, School of Medicine, University of Crete, 71003 Heraklion, Crete, Greece; [4]Department of General Surgery, Croydon University Hospital, CR7 YE London, UK; [5]Laboratory of Clinical Virology, Medical School, University of Crete, 71003 Heraklion, Crete, Greece; [6]Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, CT 06520, USA

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Abstract. The purpose of this study was two-fold, first to investigate the association between endometriosis and the risk of benign gynecologic tumors and, secondly, to evaluate the distribution of endometrioma and ovarian cysts in women with endometriosis. The medical and pathological reports of 1,000 women with endometriosis were retrospectively reviewed. The incidence of ovarian cysts, uterine leiomyomas and adenomyosis, as well as the side of ovarian cysts were further compared. A total of 295 cases of endometriomas, 172 cases of adenomyosis, 173 cases of ovarian cysts and 89 cases of uterine leiomyomas were confirmed histologically in patients with endometriosis. Serous cysts represented the most frequent diagnosis (n=81, 8.1%) in women with ovarian cysts, followed by dermoid cysts (n=15, 1.2%). In women with unilateral endometriomas, the observed proportion of left-sided cysts was found in 65.6% (164 of 250), significantly higher compared with right-sided cysts (86 out of 250, 34.4%) (P<0.001). Moreover, patients with other ovarian cysts were recognized as left-sided in 60% (96 out of 160) of cases, significantly higher compared with right-sided cysts (64 out of 160, 40%) (P<0.01). On the whole, the current study indicates that endometriosis may be associated with an increased risk of benign gynecological tumors, such as ovarian cysts, adenomyosis and leiomyomas. The results of this study confirm a left lateral predisposition of endometriomas and ovarian cysts.

Correspondence to: Dr Michail Matalliotakis, Department of Obstetrics and Gynecology, Venizeleio and Pananio General Hospital of Heraklion, Knossos Avenue, 71409 Heraklion, Greece
E-mail: mihalismat@hotmail.com

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Introduction

Endometriosis is a common, yet enigmatic gynecological disorder affecting 3-43% women of reproductive age. Endometrioma is defined as the formation of an ovarian cyst with epithelial lining resembling the ectopic endometrium. It is observed in 17-44% of women suffering from endometriosis and represents 35% of benign ovarian cysts requiring surgery (1,2). Ovarian endometriomas are the third most common site for the manifestation of endometriosis after the pouch of Douglas and uterosacral ligament (2). They are associated with an advanced stage of endometriosis involving simultaneously other pelvic or abdominal structures, as exclusive ovarian disease is found in only 1.06% of 1,785 patients with endometriosis (3). Ovarian cysts and uterine leiomyomas represent a major source of gynecological morbidity in women of reproductive age. Both conditions are included among the top 5 leading causes of hospitalization for gynecological conditions unrelated to pregnancy in women aged between 15 and 44 years (4). Leiomyoma is characterized by uterine fibroids that are non-cancerous growths of muscle tissue in the uterus (and occasionally nearby) (5). Nowadays, it is believed that dysregulated mechanistic target of rapamycin (mTOR) signaling is a major component of leiomyoma etiology, considering that an activated mTOR signaling pathway is essential for fibroid growth (6).

Adenomyosis is a common gynecological disorder which is not yet well understood; it is a myometrial lesion characterized by the presence of ectopic endometrial glands and stroma located deep within the surrounding myometrium with adjacent myometrial hyperplasia and hypertrophy (7). For over 90 years, endometriosis and adenomyosis were considered as the same entity with the exception of endometriomas. The prevalence of adenomyosis ranges from 10 to 70% according to the applied diagnostic criteria (8). It is more often observed in women aged between 30-50 years. According to Vercellini *et al* (8), adenomyosis can be identified in 30-60% of cases after hysterectomy,

with the majority of females being multiparous. Adenomyosis is observed in 69-79% of cases diagnosed with endometriosis, but only in 35-55% of women diagnosed with myomas. It has been found that adenomyosis is associated with an increased risk of endometrial hyperplasia, endometrial polyps or endometrial cancer (8).

We have previously reported a left lateral predisposition of endometrioma in two different countries (9). The limited number of studies and the small number of case reports published thus far, prompted us to investigate the association between benign gynecological tumors and endometriosis, and to further evaluate the distribution of left- and right-sided ovarian cysts in women with endometriosis.

Patients and methods

The records of all patients with endometriosis treated at the Yale University Hospital from 1995 to 2005 and from the Departments of Obstetrics and Gynecology of the University Hospital of Crete and Venizeleio General Hospital from 1990 to 2016, were reviewed. In total, 1,000 women with endometriosis who underwent surgical treatment by laparoscopy or laparotomy in two different geographical locations were investigated. The data were collected by clinicians and pathologists. The stage of endometriosis was scored according to the revised classification of the American Fertility Society (10). The clinicopathological characteristics of the benign gynecological tumors were further classified as previously described (11).

The study protocol was approved by the human subjects review boards at the two field centers. The Human Committee of Yale University School of Medicine approved the study for this evaluation (HIC #12590), as well as the Department of Obstetrics and Gynecology of the University of Crete and the Obstetrics and Gynecology of the Venizeleio General Hospital of Crete. The Ethics Committee for Human Research of Venizeleio Hospital also approved the study (ECHR #46/6686). All patients provided written informed consent prior to participation.

Data were recorded, including age, symptoms, stage of endometriosis, side (location, left or right side) and classification of cysts. Moreover, the information of the histological type of benign gynecological tumors was obtained from pathological records. In cases where two or more cysts were presented in the same gonad, we included the cases with the largest diameter (8). According to the findings, the patients were divided into 4 groups as follows: i) Ovarian or paraovarian cysts; ii) uterine leiomyomas; iii) adenomyosis; and iv) combination of all the above. The results are reported as the means ± standard deviation or as percentages where appropriate. The frequency of left- and right-sided ovarian cancer was analyzed using the χ^2 test to compare observed and external events. A P-value <0.05 was considered to indicate a statistically significant difference.

Results

Among the 1,000 females with endometriosis, endometriomas were mostly observed (29.5%), followed by adenomyosis and uterine leiomyomas (17.2 and 8.9%), respectively (Table I).

Table I. Confirmation of benign gynecological conditions in 1,000 women with endometriosis[a].

Condition	No. (%)
Ovarian or paraovarian of cyst	
Endometrioma	295 (29.5)
Serous cysts	81 (8.1)
Mucinous cysts	14 (1.4)
Dermoid cysts	15 (1.5)
Brenner tumors	13 (1.3)
Miscellaneous	28 (2.8)
Paraovarian cysts	22 (2.2)
Endometrioma and other cysts	11 (1.1)
Uterine leiomyomas	89 (8.9)
Adenomyosis	172 (17.2)
Endometrial polyps	16 (1.6)
Adenomyosis and leiomyomas	111 (11.1)
Leiomyomas and cysts	16 (1.6)
Adenomyosis and cysts	16 (1.6)
Adenomyosis, leiomyomas and cysts	15 (1.5)

Out of the 1,000 women diagnosed with endometriosis, 914 were confirmed to suffer from benign conditions. The remaining women, had endometriosis with other (not benign) conditions.

The patients with adenomyosis were the oldest (42±3.6 years) (Table II). The clinical characteristics of all women are presented in Table II. Infertility (47.8%) was mostly observed in women with endometriomas. Additionally, adnexal mass (69.4%) was found in patients with ovarian cysts and furthermore, pelvic pain was found mostly (53.5%) in women with adenomyosis. In the patients with unilateral endometriomas, the observed proportion of left-sided cysts was found in 65.6% (164/250), significantly greater compared with right-sided cysts 34.4% (86/250) (χ^2=31.2; P<0.001) and significantly different from the expected incidence of 50% (P<0.001) (Table II). Additionally, other ovarian cysts in women with endometriosis were detected left-sided in 60% (96/160) of cases, notably higher compared with right-sided cysts (64/160, 40%) (P<0.01) and significantly different from the expected incidence of 50% (P<0.01) (Table II). Of not, in the cases with ovarian cysts, the serous cyst was the most common (8.1%), followed by dermoid (1.5%) (Table I).

Discussion

Endometriosis, ovarian cysts, adenomyosis and uterine myomas are benign diseases that commonly affect women of reproductive age. Inflammatory, environmental and genetic factors play a role in the development of these benign tumors and sometimes may be found in the same women (12,13).

Previous studies have suggested that a comorbidity association exists between endometriosis and many benign gynecological tumors (4,9,12,13), although the results of certain studies differ and are unexpected. Recently, Mahnert *et al* (12) proposed that

Table II. Clinical characteristics and lateral distribution of endometrioma and ovarian cysts in the women studied.

Characteristic	Endometrioma n=295 (29.5% of total no. of women studied)	Ovarian cysts n=173 (17.3% of total no. of women studied)	Leiomyomas n=89 (8.9%) of total no. of women studied)	Ademyosis n=172 (17.2% of total no. of women studied)
Age (years)	36±5.8	38±6.2	41±4.5	42±3.6
Main complaints (%)				
Pelvic pain	120 (40.6%)	40 (19.7%)	35 (39.2%)	92 (53.5%)
Infertility	141 (47.8%)	12 (5.9%)	9 (10.1%)	62 (36%)
Adnexal mass	34 (11.6%)	141 (69.4%)	45 (50.7%)	18 (10.5%)
Left-sided	164/250 (65.6%)	96/160 (60%)		
Right-sided	86/250 (34.4%)	64/160 (40%)		
Bilateral	45	15		

Values are presented as the means ± standard deviation or n (%).

benign pre-operative surgical indications including pelvic mass, endometriosis, pelvic pain or leiomyomas were found in 2.7% of unexpected gynecological malignancies. Furthermore, Verit and Yucel (13) in a meta-analysis indicated that endometriosis, leiomyomas and adenomyosis may be associated with an increased risk of gynecological cancers, such as endometrioma and ovarian cancers. Therefore, it has been proposed that ovarian endometriomas, in most cases (90%), are formed by the invagination of the ovarian cortex. Although there seems to be a consensus regarding the invagination theory, there is still a controversy between the implantation theory and the metaplasia theory. However, an article published by Nisolle and Donnez (14), suggested that the mesothelium covering the ovary may invaginate into the ovarian cortex. Motta *et al* (15) also described invaginations of the mesothelial layer covering the ovarian surface. These mesothelian inclusions may be transformed into intra-ovarian endometriosis by metaplasia, under the influence of unknown factors.

The complexity of the disease and the limited progress in identifying its exact cause explain the reason for the existence of so many controversies in the literature regarding the most effective modality to treat endometriomas. In our series, we observed that endometriomas represented the most common type (29.5%), followed by ovarian cysts (20.3%), adenomyosis (17.2%) and uterine leiomyomas (8.9%). The current data indicate that women with endometriosis should be counseled about the future risks of developing these benign gynecological diseases. To the best of our knowledge, this is the first study on 1,000 women with endometriosis and the simultaneous co-existence of benign gynecological tumors. Despite the various theories developed to explain the establishment of endometriosis, there is a great deal of evidence to suggest that endometriosis is result of a poly-parametric system with multiple origins. In the current study, we found unilateral endometrioma was more frequent on the left-sided (65.6%) than the right-sided (34.4%) ovary. Moreover, in women with other ovarian cysts, the location site was were observed to be mostly on the left side (60%), significantly higher compared with the right side (40%).

Our results are in agreement with those of our previous study, in which it was reported that the majority of endometriomas were located in the left ovary. In that study, we suggested a new mechanical theory of implication, the female varicocele theory, which could play an important role in the development of ovarian endometriosis or endometriomas (9). These and previous results are in accordance with those of other studies (16-18), where it is observed that the left side of the pelvis is more frequently affected, possibly as the presence of the sigmoid colon reduces peritoneal fluid movement.

Considering that endometriosis arises from the interplay between genetic and environmental factors, various studies (described below) have attempted to elucidate whether any shared genetic factors exist for endometriosis, leiomyoma and adenomyosis or the genetic basis is very specific for each condition.

Various scenarios have been suggested thus far regarding the histogenesis of adenomyosis and the molecular pathways involved in this procedure. Thus, a study focusing on adenomyosis tissue reported that specific uterine marker molecules are expressed, such as oxytocin receptor (OTR), vasopressin receptor (VPR), estrogen receptor (ER) and progesterone receptor (PR) (19). Considering that angiogenesis represents an important factor in the development of adenomyosis, various growth factors, as well as a genetic polymorphism of fibroblast growth factor 2 (*FGF-2*) have been suggested to be associated with the development of this condition (20). Moreover, the loss of heterozygosity (LOH) in DNA mismatch repair genes in adenomyosis has been reported by our group previously (21). A difference has been observed regarding the expression levels of ER and PR between the adenomyosis and leiomyoma. Of note, it was found that ER-β expression and the lack of PR expression lead to the development of adenomyosis (22). Metalloproteinases (MMPs) consist a group of enzymes that mediate the degradation of most extracellular matrix proteins during organogenesis, growth and normal tissue turnover. Whilst their very low expression and activity in normal adult tissues (23), in patients with leiomyoma and/or adenomyosis MMPs as well as some specific cytokines have been found at significantly elevated levels (24).

The peroxisome proliferator-activated receptor-γ (*PPAR-γ*) 161CC genotype was found to be a risk factor for adenomyosis

and endometriosis, but not for leiomyoma (25). The 3 bp I/D polymorphism of the *CYP19* gene showed an association with endometriosis, but not with the adenomyosis/leiomyoma subgroup (26). The +2073 A/T polymorphism of *EGFR* gene (27) and the *ACE* I/D polymorphism (28) were found to be associated significantly with endometriosis and leiomyoma. Furthermore, the *VEGF* -1154GG genotype (29), two MMP-1 polymorphisms (30) and the -181 A/G polymorphism of MMP-7 (31) were found to be associated with endometriosis and adenomyosis.

Taken together, the aforementioned findings point out that some genetic factors may exhibit a pleiotropic effect concerning these conditions, thus being common risk factors for more than one of them.

In conclusion, the present study demonstrates that endometriosis is linked with an increased risk of benign gynecological tumors, such as ovarian cysts, adenomyosis and uterine leiomyomas. Additionally, the present data confirmed a left lateral predisposition of endometrium and other ovarian cysts. Overall, further research and investigations are required to elucidate the correlation between endometriosis and benign gynecological morbidities.

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