

Association between Endometrioma and Die and Other Gynecological Disease such as Endometrial Polyp, Myomas and Adenomyosis in Ultrasonography

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ABSTRACT

Background: Endometriosis, endometrial polyps, adenomyosis, and uterine fibroids are benign diseases affecting women in reproductive years. The similar characteristics and common estrogen-dependent mechanisms of endometriosis with other disorders favor an association between them.

Methods: In this cross-sectional study, we reported the prevalence of endometrial polyps, adenomyosis, and fibroids in women with endometriosis and then, investigated the possible associations between them. 153 women diagnosed with endometriosis were included. Demographic, anthropometric, and gynecologic characteristics along with their symptoms were recorded. Also, Sonographic indices of uterine and adnexes, DIE, and soft markers were recorded.

Results: Investigating symptoms, 97.4% of them experiences dysmenorrhea. Abdominal pain is much more prevalent than back pain among patients with endometriosis. Dyspareunia is reported to be as high as 60.5%. Our study showed 30.3%, 25.5%, and 10.5% of the prevalence of adenomyosis, uterine fibroids, and endometrial polyps in patients with endometriosis. In addition, a positive association between adenomyosis and DIE, between endometrial polyps and endometriosis severity, a negative correlation between endometriomas and endometrial polyps and between adenomyosis and endometriosis severity reported in our study.

Conclusion: Due to the remarkable relationship between DIE and adenomyosis, having more information about adenomyosis, either diagnostic and therapeutic, along with timely treatment could prevent endometriosis.

Keywords: Endometriosis, myoma, endometrial polyp, adenomyosis.

INTRODUCTION

Endometriosis, endometrial polyps, adenomyosis, and uterine fibroids are benign diseases that commonly affect women during their reproductive years¹. Endometriosis is defined by the presence of endometrial glands and stroma at extra-uterine locations. It affects approximately 5%–10% of women in reproductive age and is found in up to 20%–50% of infertile women². Endometriosis results in dysmenorrhea, pelvic pain, infertility and decreased quality of life³. Many women, however, remain free of symptoms or exhibit only minor complaints⁴.

On the other hand, ovarian endometriotic cysts, known as endometriomas, require special attention because of their association with advanced endometriosis and infertility, which usually requires surgical intervention⁵. Another type of endometriosis known as Deep Infiltrating Endometriosis (DIE) penetrates into sub-peritoneum or other sites in the pelvis (6). Since the improvement of diagnostic accuracy using invasive intervention, the incidence of endometriosis is getting even more⁷; However, transvaginal ultrasonography seems to be sensitive and specific enough when done by an experienced radiologist, to make the diagnosis and exclude other differential diagnoses⁸.

Endometrial polyps, the localized endometrial intrauterine overgrowth, can affect up to 25% of women, especially infertile women⁹. They may be single or multiple, may measure from a few millimeters to centimeters, and may be sessile or pedunculated¹⁰. Endometrial polyps usually result in abnormal uterine bleeding and infertility, but sometimes they could be asymptomatic^{11,12}.

Adenomyosis is a benign condition defined by the growth of endometrial glands in the myometrium¹³. Its prevalence is estimated to be at a wide range, due to difficulty in diagnosis, between 5 to 70 percent, with a mean of 20–30%^{14,15}. Commonly, adenomyosis could cause dyspareunia, dysmenorrhea, abnormal uterine bleeding, and infertility¹⁶. Leiomyomas are the most associated pathology with adenomyosis, that could make the management complex. Usually the full adenomyosis need hysterectomy as treatment, which also make the diagnoses much more accurate.

Uterine fibroids are estimated to occur in 33–77% of women at reproductive age¹⁷. Although most uterine fibroids are asymptomatic, they are still the most common reason for hysterectomy¹⁸. Common symptoms of fibroids include menorrhagia, pelvic pressure/pain and urinary symptoms according to their size, number and location in the uterus¹⁹. The similar characteristics and common pathological mechanisms of endometriosis with endometrial polyps, adenomyosis, and uterine fibroids suggest a possible association between these benign gynecological conditions. It is not known whether any of them could act as a risk factor of the other one. Besides, to the best of our knowledge, no report in the literature had investigated these associations simultaneously. In this study, we reported the prevalence of endometrial polyps, adenomyosis and fibroids in women with endometriosis and then, investigated the possible associations between them.

MATERIALS AND METHODS

This cross-sectional study aimed to assess the prevalence and association of uterine diseases, including endometrial polyps, adenomyosis and uterine fibroids with endometriosis. 153 women diagnosed with endometriosis between the years 2017 to 2019 at Hazrat Rasool Akram Hospital, Tehran were included. Endometriosis diagnosis was made by transvaginal or transrectal ultrasonography. Even though the definitive diagnosis of endometriosis requires invasive intervention (laparoscopic procedure or open surgery), transvaginal or transrectal ultrasound seems to be a useful diagnostic test, when done by an experienced radiologist (8). The study exclusion criteria included a history of endometrial polypectomy or myomectomy, being under treatment for adenomyosis and patients undergoing hormone therapy or OCP. The following demographic, anthropometric and gynecological characteristics were recorded: age, height, weight, gravidity and parity (number of all prior pregnancies, spontaneous abortions, terminations of pregnancy and live births including the mode of delivery), breastfeeding history, menarche age, menstrual cycle duration and regularity, history of previous surgery. Also, different systems symptoms including constitutional presentations (fatigue, pelvic pain and tenderness), GI symptoms (nausea, diarrhea, and constipation), gynecological symptoms (abdominal pain, back pain, dyspareunia, dysmenorrhea), urinary presentations (dysuria, frequency, and hematuria) were recorded. Body mass index (BMI) was calculated based on their measured height and weight using a calibrated scale and stadiometer. The level of patient's discomfort/pain was evaluated by the visual analog scale (VAS) system, utilizing a 5 cm line with the extreme points 0 and 5 corresponding to "no pain" and "maximum pain," respectively. Then transvaginal ultrasonography in non-virgins and transrectal ultrasonography in virgins were carried out blindly by a single experienced sonographer who had examined over 20000 patients with various gynecological complaints and passed comprehensive training on the ultrasonographic diagnosis of uterine disorders. We used a high-quality ultrasonography device (Philips, Affinity 70) equipped with a transvaginal 3-10 Hz transducer, with a curved vaginal probe. It was performed based on the systematic protocol introduced by the International Deep Endometriosis Analysis (IDEA) Consensus Group, as described before²⁰.

Sonographic indices, including uterine and adnexes, DIE (Bladder type, Intestinal type, Douglas pouch obliteration and Adnexal adhesions), sliding sign, soft markers like localized tenderness were recorded. Also, uterine fibroma with their location according to the FIGO criteria, endometrial polyps with their sizes and adenomyosis with their severity were recorded. The severity of endometriosis was defined according to AFS criteria²¹.

Statistical analysis: Qualitative Variables reported as count (percent) and quantitative variables reported as mean (standard deviation). Kolmogorov Smirnov test was used to assess the normal distribution of variables. To compare two normally-distributed dichotomous variables, the chi-square test was used. Fisher's exact test was used

when data were not normally distributed. For investigating the association between variables Pearson correlation or Spearman correlation test was done, where appropriate according to the variable. Data were analyzed by SPSS software version 24. P value<0.05 considered significant in all of the tests.

Ethical considerations: This study was approved by the ethical committee of Iran University of Medical Science. (Project number: IR.IUMS.FMD.REC.1399.052) and after explaining the study protocol for the patients, written informed consent were obtained from participants.

RESULTS

We recruited 153 patients diagnosed with endometriosis in the study. The mean age of participants was 32.41 (6.22) and 74% of them were married. On average, they experience their menarche at 13.09 (1.53) years. 35.6%, 60% and 4.4% of them have one child, two and three children, respectively. 77.9% of them have regular menstrual cycles and the majority of them (74%) have menstrual cycle lasting 21 to 35 days and most of them (65.3%) experience menstrual bleeding lasting 3 to 7 days. None of them has more than seven days of menstrual bleeding.

Investigating their symptoms, 97.4% of them experiences dysmenorrhea. Among patients reporting dysmenorrhea, half of them said that they always experience it. Abdominal pain is much more prevalent than back pain among patients with endometriosis. Having pain at the time of intercourses, named dyspareunia, is reported to be as high as 60.5% in these patients; however, most of them reported its severity less than 3 out of 5 (72.3%). About half of them reported fatigue (67.3%), chronic pelvic pain (47.7%) and constipation (40.3%); however, the prevalence of other symptoms was much less.

As mentioned before, all of the patients were diagnosed with endometriosis by an expert sonographer. We, then assess the co-existence of other gynecological problems with endometriosis. As table 2 showed, 84.3% of patients with endometriosis had endometrioma. Moreover, 60% of them were one-sided endometrioma. Also, we examine patients for the existence of DIE, another subtype of endometrioma. 63.3% and 54% of them showed the sub-peritoneal and intestinal types of DIE, respectively. Also, 30.3%, 25.5% and 10.5% of them reported having adenomyosis, uterine fibroid, and polyps in addition to their previously diagnosed endometriosis, respectively. Most of the diagnosed adenomyosis (93.5%) were mild. The majority of uterine fibroids (65%) were subserosal and intramural, each counting for 32.5% of uterine fibroids. Also, we assess the patients for two important sonography findings, adnexal adhesion, and Douglas pouch obliteration. Evaluating the patients for adnexal adhesion severity showed that slightly half of them have moderate severity. Similarly, sonography findings of most of the patients showed moderate obliteration for Douglas pouch.

Next, to investigate the association of coexisting conditions with each other, we analyzed the subgroups prevalence and correlations. Table 3 presents the results. We found a significant negative correlation between endometriomas and endometrial polyps ($\hat{\alpha}=-0.209$,

P=0.01). The prevalence of endometriomas was higher in patients without polyps (66%) in comparison with patients with polyps (33%) (P=0.027). Moreover, adenomyosis showed a significant positive correlation with two types of DIE, bladder and intestinal ($\hat{\alpha}$ =0.234 and 0.169, P=0.004 and 0.037, respectively). Patients with adenomyosis had a greater prevalence of bladder and intestinal DIE (11% and 46%) in comparison with patients without adenomyosis (0.9% and 28%) (P=0.01 and 0.04, respectively). None of the other correlations was significant, especially

endometrioma, unlike DIE, was not correlated with adenomyosis. Moreover, as the last three row of table 3 showed, adnexal adhesion severity was significantly associated with the incidence of adenomyosis, where the prevalence of severe adnexal adhesion in patients with adenomyosis (43%) was higher than the patients without it (20%) (p=0.016). also, the endometriosis severity was significantly associated with incidence of endometrial polyps and adenomyosis.

Table 1. Demographic, anthropometric and gynecologic characteristics of participants

Demographic and anthropometric characteristics	n=153	Gynecologic Symptoms	n=153
Age (y) (mean \pm SD)	32.41 \pm 6.22	Dysmenorrhea (Y) (N [%])	150 (97.4%)
Weight (Kg) (mean \pm SD)	63.22 \pm 10.26	Dysmenorrhea frequency (N [%])	
Height (cm) (mean \pm SD)	164.27 \pm 5.94	Sometimes	38 (25.9%)
BMI (kg/m ²) (mean \pm SD)	24.18 \pm 9.26	Seldom	35 (23.8%)
Marital status (N [%])		Always	74 (50.3%)
Single	37 (24%)	Dysmenorrhea severity (out of 5) (N[%])	
Married	114 (74%)	1	3 (2%)
Divorced	3 (1.9%)	2	16 (10.6%)
Hx of surgery due to endometriosis (Y)	24 (15.9%)	3	43 (28.5%)
Age at menarche (y) (mean \pm SD)	13.09 \pm 1.53	4	59 (39.1%)
Middle day of menstrual cycle (d) (mean \pm SD)	12.83 \pm 7.24	5	29 (19.2%)
Cycle duration (N [%])		Abdominal pain (N [%])	141 (91.6%)
Less than 21 days	29 (19.3%)	Back Pain (N [%])	75 (48.7%)
21 to 35 days	111 (74%)	Dyspareunia (N [%])	75 (60.5%)
More than 35 days	10 (6.7%)	Dyspareunia severity (N [%]) (out of 5)	
Duration of menstrual bleeding (N [%])		1	4 (5.3%)
Less than 3 days	50 (34.7%)	2	20 (26.3%)
3 to 7 days	94 (65.3%)	3	31 (40.8%)
Regular menstruation cycles (N [%])	120 (77.9%)	4	16 (21.1%)
Number of deliveries (mean \pm SD)	1.63 \pm 0.53	5	5 (6.6%)
One child (N [%])	16 (35.6%)	Dyspareunia timing (N [%])	
Two children (N [%])	27 (60%)	Initial	67 (88.2%)
Three children (N [%])	2 (4.4%)	Terminal (deep)	42 (55.3%)
Constitutional symptoms		Gastrointestinal symptoms	
Periodic pelvic pain (Y) (N [%])	72 (47.7%)	Diarrhea (Y) (N [%])	18 (11.7%)
Pelvic pain severity		Constipation (Y) (N [%])	62 (40.3%)
No pain	5 (8.5%)	Nausea (Y) (N [%])	17 (11.1%)
Mild	17 (28.8%)	Pain during defecation (Y) (N [%])	35 (22.9%)
Moderate	25 (42.4%)	Urinary symptoms	
Severe	12 (20.3%)	Urinary frequency (Y) (N [%])	35 (22.9%)
Fatigue (Y) (N [%])	103 (67.3%)	Dysuria (Y) (N [%])	12 (7.8%)
Tenderness during sonography (N [%])	35 (22.9%)	Hematuria (Y) (N [%])	3 (2%)

Table 2. Prevalence of associated conditions and their types in patients with endometriosis

Endometriosis subtypes	n=153	Other Conditions	n=153
Endometriosis severity		Adenomyosis (N [%])	46 (30.3%)
Minimal	12 (7.8%)	Adenomyosis degree (N [%])	
Mild	10 (6.5%)	Mild	43 (93.5%)
Moderate	58 (37.9%)	Severe	3 (6.5%)
Severe	72 (47.1%)	Uterine fibroid (N [%])	39 (25.5%)
Endometrioma (N [%])	129 (84.3%)	Locations of Uterine fibroid (N [%])	
Type of Endometrioma (N [%])		Subserosal	13 (32.5%)
One-sided	79 (60.8%)	Intramural	13 (32.5%)
Two-sided	51 (39.2%)	Intramural with extension to subserous	1 (0.6%)
Deep Infiltrating Endometriosis (DIE) \ (N [%])		All locations	13 (8.4%)
Bladder	4 (2.6%)	Endometrial Polyps (N [%])	16 (10.5%)
Intestinal	54 (35.3%)		
Sub-peritoneal	93 (63.3%)		
Important sonography findings		Douglas pouch obliteration severity (N [%])	
Adnexal adhesion severity (N [%])		Mild	53 (35.3%)
Mild (less than one-third)	41 (28.9%)	Moderate	76 (50.7%)
Moderate (one-third to two-third)	62 (43.7%)	Severe	21 (14%)
Severe (more than two-third)	39 (27.4%)		

Table 3. Correlation between associated conditions and their prevalence within each condition

Conditions	Endometrioma	Endometrial Polyp	Uterine fibroid	Adenomyosis	Bladder DIE	Intestinal DIE
Endometriomas		16 (12.4%)	33 (25.6%)	41 (32%)	#	#
Endometrial Polyps	-0.209*					
Uterine fibroids	0.005	0.045				
Adenomyosis	0.089	-0.026	0.05			
Bladder DIE	#			0.234*		#
Intestinal DIE	#			0.169*	#	
Adnexal adhesion (severe/ not severe)		-0.036	-0.033	-0.231*		
Douglas pouch obliteration severity		-0.053	-0.025	0.138		
Endometriosis severity		0.184*	0.016	-0.164*		

*Significant at P<0.05 using Chi-square test.

*Data is presented as Pearson R in the lower left of the Table and count (percent) at the upper right part of the table.

-Note that values presented in the upper right cells were the number of patients showing both of the conditions in the row/column and the percentage of having the condition in the column in patients with the condition in the row. Cells marked with # are subtypes of endometriosis, and their correlations were not considered meaningful.

DISCUSSION

This study was designed to evaluate the prevalence of some benign uterine disorders and the association between them in women with endometriosis.

First, we reported demographic and anthropometric characteristics of the patients, along with gynecological and systemic symptoms. We found that almost all of our patients complained of dysmenorrhea. Other pain symptoms such as abdominal pain, dyspareunia and back pain had reported to be the most common symptoms, thereafter.

Considering that all of our participants were diagnosed with endometriosis, the prevalence of endometrioma, adenomyosis, fibroma and uterine polyps were 84.3%, 30.3%, 25.5% and 10.55, respectively. In patients with endometriosis, it seems that the prevalence of endometrioma was higher, and the prevalence of polyps was lower compared with the general population (15, 22-25). Considerably, most of the endometrioma found in these patients were two-sided. Adenomyosis was the most common benign disorder found in women with endometriosis. Similar to our study, Two other studies investigating adenomyosis in women with endometriosis, reported its prevalence in the range of 27-47.8%^{26,27}. Importantly, to best of our knowledge, this is the first study to this date, reporting the prevalence of endometrioma and deep infiltrating endometriosis, together, with other uterine disorders, enabling us to assess their associations.

We found a significant positive association of adenomyosis with DIE. Consistent with our results, Midgley et al. found a correlation between adenomyosis and rectosigmoid deep infiltrating endometriosis (28). Moreover, other studies reported a significant association between adenomyosis and peritoneal DIE in infertile women^{26,29,30}. A negative association between endometrioma and endometrial polyps was found in this study. Higher incidence of endometrioma and lower incidence of polyps in women with endometriosis contributed to their negative association. This association was not discussed previously. Although we did not find any significant association between other disorders, other studies reported some; for example; Shen et al. in 2011 in a retrospective study on 413 infertile women, indicated a high prevalence of

endometrial polyps in women diagnosed with endometriosis². Also, Umari et al. in 2011, suggested an association between uterine fibroids and endometriosis⁷. This difference in results could be due to racial and ethnical characteristics of each population.

Some of the papers, consider the similar pathogenesis of these disorder as the underlying factor for the association. Although the exact pathogenesis of endometriosis is unclear, it is considered to be an estrogen-dependent disorder³². Notably, all of these uterine disorders are also believed to be an estrogen-dependent disease, similar to endometriosis³³. The expression patterns of estrogen receptors (ER) and aromatase are altered in patients with endometriosis³⁴. The concentrations of estrogen and progesterone receptors were found to be significantly higher in the endometrium of a woman with endometrial polyps than in normal endometrium³⁵. Moreover, the endometrium aromatase level was remarkably higher in patients with endometrial polyps than healthy individuals. Therefore, estrogen metabolism in the endometrium of these patients is completely different from that in healthy individuals^{3,36,37,38}.

Previous study reported that adnexal adhesions are more common in patients affected by endometriosis (30). In this study, a positive correlation was found between the existence of adenomyosis and adnexal adhesions, where severe adnexal adhesion was more common in patients with adenomyosis. Further study is needed to assess the exact effect of adenomyosis on adnexal adhesions.

Also the endometriosis severity was significantly higher in patients with adenomyosis and endometrial polyps. A study in 2007 reported that the incidence of endometrial polyps in patients with moderate endometriosis were higher than patients with severe endometriosis³⁹. Moreover a recent prospective study, on 234 women who underwent laparoscopic surgery, showed that patients who has sonographic evidence of adenomyosis were more likely to have severe endometriosis and its markers such as DIE⁴⁰.

CONCLUSION

Endometriosis and its subtypes, endometrioma and DIE, could accompany other benign uterine disorders. Our study

showed 30.3%, 25.5% and 10.5% of prevalence of adenomyosis, uterine fibroids and endometrial polyps in patients with endometriosis. A positive association between adenomyosis and DIE, between endometrial polyps and endometriosis severity, and between adenomyosis and endometriosis severity, a negative correlation between endometriomas and endometrial polyps reported in our study, which requires further investigation. Due to remarkable relationship between DIE and adenomyosis, having more information about adenomyosis, either diagnostic and therapeutic, along with timely treatment could prevent endometriosis.

Strengths and limitations: The cross-sectional method of study is one of the limitations, preventing us from assessing the risk factors and causality relationships. Another limitation is the lack of histological verification of diagnoses, although, a high agreement was reported between diagnostic ultrasonography of some uterine disorders and histological findings⁴¹.

The main strength of the study is that, to best of our knowledge, this is the first study to this date which evaluated the prevalence of endometrioma and deep infiltrating endometriosis, along with other uterine disorders. Another strength is the large sample size in comparison to other studies and absence of comprehensive study to assess the mentioned factors in Iranian population.

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