

Adenomyosis: prevalence, risk factors, symptoms and clinical findings

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Summary

Objective: This prospective study investigated the prevalence of adenomyosis in histopathological examinations of patients who had undergone hysterectomy due to various indications in our clinic. Epidemiological characteristics, predisposing risk factors, symptoms and clinical findings of adenomyosis were evaluated.

Method: A total of 298 subjects who had undergone abdominal, vaginal or laparoscopic hysterectomy with/without salpingo-oophorectomy between October 2003 and April 2004 in our clinic were included. Uterine specimens obtained through hysterectomy were weighed and histopathologically examined in the Pathology Department of Ege University. The study group (n = 103), cases with adenomyosis, was compared with the control group (n = 195), cases without adenomyosis, with respect to the epidemiological, clinical and histopathological characteristics.

Results: The prevalence of adenomyosis in 298 subjects was 36.2% (103). Duration of the reproductive period in patients with adenomyosis was found to be significantly longer than for those in the control group ($p < 0.05$). Prevalence of pelvic pain, dysmenorrhea and dyspareunia was also significantly higher in the study group ($p < 0.05$). Moreover, the number of cases requiring blood transfusion before the operation was significantly higher in the study group ($p < 0.05$) as were the rates of smoking, previous uterine surgery and nulliparity ($p < 0.05$). The most common gynecological condition accompanying adenomyosis was found to be uterine myoma in both groups, but the difference was not significant.

Conclusion: Adenomyosis is not a rare histopathological finding. Due to diagnostic and therapeutic methods which are being developed as an alternative to hysterectomy, the clinical effects of adenomyosis and its association with other gynecological conditions, adenomyosis appears to be an issue which will be more intensively investigated in the future.

Key words: Adenomyosis uteri; Prevalence; Risk factors; Symptoms; Clinical findings.

Introduction

Adenomyosis, also known as endometriosis interna, is defined as the presence of endometrial tissue within the myometrium. The interest in adenomyosis has increased due to the results of recent studies where adenomyosis was reported to present symptoms such as pelvic pain, dysmenorrhea and irregular menstruation, as well as being involved in etiologies of infertility and early abortion [1].

Similarities between adenomyosis and endometriosis, with respect to the symptoms, clinical outcomes and theories related to their etiopathogenesis have been reported in recent studies [2]. However, adenomyosis has some basic histopathological differences from endometriosis. Glandular and stromal structures in adenomyosis have been shown to be similar to basal endometrium by histological and immunohistochemical studies. For this reason, response to hormonal stimulation is rare in adenomyotic foci and repetitive symptoms and findings peculiar to the menstrual period are not observed, whereas the endometrium within an endometriotic focus has a functional characteristic with repetitive symptoms and findings [3, 4].

Adenomyosis, with symptoms and clinical outcomes similar to endometriosis, draws considerable attention, particularly due to the need for the development of alter-

native diagnostic and therapeutic methods because of its role in the etiology of infertility and the absence of a consensus on the prevalence and etiopathogenesis of this disorder, which is still not clear. However, the number of studies on adenomyosis are few when compared with endometriosis.

The purpose of this study was to investigate the prevalence, epidemiological characteristics, predisposing risk factors, associated clinical and histopathological conditions, symptoms and clinical findings of adenomyosis.

Material and Method

A total of 298 subjects who had undergone abdominal, vaginal or laparoscopic hysterectomy with or without adnexa between October 2003 and April 2004 in our clinic were included in the study. Written informed consent was obtained from each woman before surgery using the consent forms and protocols approved by the Human Investigation Committee of Ege University.

Uterine specimens obtained through hysterectomy were weighed and histopathologically examined in the Pathology Department of Ege University. Full-thickness cross-sections were obtained from the anterior, posterior and lateral walls of all uterine specimens for histopathological examination. Adenomyosis was defined as the presence of endometrial glands and stroma within the myometrium, at least 2 mm below the endo-myometrial junction, and in the presence of surrounding myometrial hyperplasia.

Through histopathological examination, adenomyosis was diagnosed as alone or associated with other gynecological conditions in 103 subjects (study group), while no adenomyosis was observed in the remaining 195 subjects (control group).

The patients in both the study and control groups were compared with respect to epidemiological characteristics and predisposing risk factors such as age, menopausal status, duration of reproductive period, parity, smoking habits, early abortion and infertility; symptoms such as bleeding disorders, pelvic pain, dysmenorrhea, dyspareunia and anemia; history of previous uterine surgery; indications for hysterectomy and histopathological findings.

Obtained data were statistically analyzed using SPSS software. The chi-square test was used for the comparison of categorical values, while a special test, namely Fisher's exact test, was used when the tables were in a 2 x 2 situation. Significance was determined as $p < 0.05$.

Results

The prevalence of adenomyosis uteri was determined as 36.3%. The age of women included in the study group ranged from 39 to 86 years (average of 50.03 ± 10.4) whereas in the control group it was 38 to 71 years (average of 49.5 ± 5.7). The epidemiological characteristics, predisposing risk factors, symptoms, clinical findings and history of previous uterine surgery are summarized in Table 1.

Table 1. — Patient characteristics and symptoms.

Patient characteristics	Study group (n: 103)	Control group (n: 195)	p
Age (years)	50.3 ± 10.4	49.5 ± 5.7	> 0.05
Reproductive period (years)	33.91 ± 13.3	32.10 ± 7.1	< 0.05
Menopause	31 (30.1%)	79 (40.5%)	> 0.05
Oligomenorrhea	4 (3.9%)	6 (3.1%)	> 0.05
Regular menstruation	21 (20.4%)	40 (20.5%)	> 0.05
Nulliparous	22 (21.4%)	20 (10.3%)	< 0.05
Smoking	37 (35.9%)	47 (24.1%)	< 0.05
Previous history			
of uterine surgery	63 (61.2%)	88 (45.2%)	< 0.05
Primary infertility	2 (1.9%)	9 (4.6%)	> 0.05
Secondary infertility	5 (4.6%)	6 (3.6%)	> 0.05
Early pregnancy loss	11 (10.67%)	21 (10.7%)	> 0.05
One early abortion	2 (1.9%)	4 (2.1%)	> 0.05
Two early abortion	7 (6.8%)	15 (7.7%)	> 0.05
Three or more early abortion	2 (1.9%)	2 (1.0%)	> 0.05
Anemia	22 (21.4%)	22 (11.3%)	< 0.05
Severe anemia	5 (4.9%)	4 (2.1%)	< 0.05
Blood transfusion	14 (13.6%)	8 (4.1%)	< 0.05
Symptoms			
Menometrorrhagia	47 (45.6%)	70 (35.9%)	> 0.05
Pelvic pain	33 (32.04%)	12 (6.15%)	< 0.05
Dysmenorrhea	26 (25.2%)	27 (13.8%)	< 0.05
Dyspareunia	19 (18.4%)	21 (10.8 %)	< 0.05

Due to the effect of estrogen on the development of adenomyosis, total duration of the reproductive periods of the subjects as the cumulative time with estrogen effect was calculated. Duration of the reproductive period was observed to be significantly higher in the study group when compared with the control group (33.91 ± 13.3 and 32.10 ± 7.1 years, respectively) ($p < 0.05$).

In the study group, when the subjects were evaluated with respect to their menstrual cycles, 45.6% (47) had menometrorrhagia, 30.1% (30) of the patients were menopausal, 20.4% (21) had regular menstruation and 3.9% (4) had oligomenorrhea, while in the control group, 40.5% (79) of the patients were menopausal, 35.9% (70) had menometrorrhagia 20.5% (40) had regular menstruation and 3.1% (6) had oligomenorrhea. No significant differences were obtained between the two groups.

Pelvic pain, dysmenorrhea and dyspareunia were significantly more common symptoms in the study group compared to the control group (32.04% (33) vs 6.15% (12), 25.2% (26) vs 13.8% (27), 18.4% (19) vs 10.8% (21), respectively) ($p < 0.05$).

When the groups were evaluated with respect to parity, the rates of nulliparity in the study and control groups were 22 (21.4%) and 20 (10.3%), respectively ($p < 0.05$). It was found that the number of parturitions did not significantly effect adenomyosis prevalence in multiparous females.

The rate of smoking was 35.9% (37) among women with adenomyosis while it was 24.1% (47) in the control group, significantly lower than the study group ($p < 0.05$). The effect of previous uterine surgery such as early pregnancy termination and cesarean section on the development of adenomyosis was also evaluated. The rate of pregnancy termination and cesarian section was 61.2% and 45.2% in the study and control groups, respectively, and this difference was found to be significant ($p < 0.05$).

When the subjects were compared for history of infertility, two subjects with primary (1.9%) and five subjects with secondary infertility (4.6%) were observed in the study group, whereas nine subjects with primary (4.6%) and six subjects with secondary infertility (3.6%) were observed in the control group. The difference between the two groups was not significant.

The number of patients with a history of an early abortion was 11 (10.67%) and 21 (10.7%) in the study and control groups, respectively. Although not significant, the number of patients with early abortion history was higher in the study group. History of one early abortion was observed in two subjects (1.9%) in the study group and four subjects (2.1%) in the control group, while a history of two early abortions was observed in seven subjects (6.8%) in the study group and 15 subjects (7.7%) in the control group, and a history of three or more early abortions (habitual abortion) was observed in two subjects (1.9%) in the study group and two subjects (1.0%) in the control group. There was no significant difference between the two groups.

When both groups were compared according to the requirement of blood transfusion before the operation, we found that the number of subjects with anemia (hemoglobin level < 12 g/dl) was 22 (21.4%) in the study group and 22 (11.3%) in the control group. However, severe anemia (hemoglobin level < 10 g/dl) was observed in five subjects (4.9%) in the study group and four subjects (2.1%) in the control group. Both anemia and severe anemia rates in the study group were found to be signifi-

icantly higher than those in the control group ($p < 0.05$). On the other hand, during the preoperative period, 14 subjects (13.6%) in the study group and eight subjects (4.1%) in the control group required blood transfusions due to severe anemia. The rate of blood transfusion was significantly higher in the study group ($p < 0.05$).

The most common indication for hysterectomy was uterine myoma, with a prevalence of 46% (47) in the study group and 35.9% (70) in the control group. No significant differences in surgical indications were observed between the two groups. All hysterectomy indications of the groups are shown in Table 2.

Table 2. — *Indications for hysterectomy.*

Indications for hysterectomy	Study group no. (%)	Control group no. (%)	p
Uterine myoma	47 (46%)	70 (35.9%)	> 0.05
Associated gynecological conditions*	15 (14%)	35 (17.9%)	> 0.05
Endometrial hyperplasia	13 (12%)	21 (10.7%)	> 0.05
Uterine prolapse	6 (6%)	17 (8.7%)	> 0.05
Adnexal mass	5 (5%)	27 (13.8%)	> 0.05
Endometrial carcinoma	5 (5%)	5 (2.5%)	> 0.05
Menometrorrhagia*	4 (4%)	6 (3.07%)	> 0.05
Pelvic pain	3 (3%)	-	> 0.05
Cervical dysplasia	3 (3%)	5 (2.5%)	> 0.05
Other gynecological malignancies	2 (2%)	9 (4.6%)	> 0.05

*: Patients with more than one indication (uterine myoma, endometrial hyperplasia, menometrorrhagia, endometriosis, adnexal mass).

†: Medical therapy-resistant.

The results obtained with the histopathological examination of the study and control groups are shown in Table 3 and Table 4, respectively. The prevalence of endometriosis in the study and control groups was 2.91% [3] and 3.07% [6], respectively. There were no significant differences in the histopathological findings between the two groups.

Table 3. — *Histopathological findings of subjects in the study group.*

Histopathological findings	no./%
Adenomyosis + uterine myoma	52/50.48%
Pure adenomyosis	25/24.27%
Adenomyosis + Endometrial hyperplasia	9/8.74%
Adenomyosis + Endometrial carcinoma	5/4.85%
Adenomyosis + Endometriosis	3/2.91%
Adenomyosis + Benign adnexal mass	3/2.91%
Adenomyosis + Endometrial polyp	2/1.9%
Adenomyosis + Cervical dysplasia	2/1.9%
Adenomyosis + Other gynecological malignancies	2/1.9%

Table 4. — *Histopathological findings of subjects in the study group.*

Histopathological findings	no./%
Uterine myoma	126/64.6%
Endometrial hyperplasia	20/10.25%
Benign adnexal mass	16/8.2%
Other gynecological malignancies	11/5.6%
Endometrial carcinoma	8/4.1%
Endometriosis	6/3.07%
Endometrial polyp	4/2.05%
Cervical dysplasia	4/2.05%

The uterine specimens were weighed following hysterectomy. The heaviest uterine specimen was 2,300 g, while the lightest was 30 g, with a mean weight of 229,90 g. The mean uterine weights in the study and control groups were 222,23 g and 233,95 g, respectively, where the difference between groups was not significant. The mean uterus weight in the subjects with pure adenomyosis was 153.09 g. Abdominal hysterectomy was performed in 257 cases (86.2%), while vaginal hysterectomy was performed in 31 (10.4%), and laparoscopic hysterectomy was performed in ten (3.4%) cases.

Discussion

The exact prevalence of adenomyosis is still not known, and different reports in the literature put it in the range of 5% to 70% [5]. The possible reasons for this wide variance include the necessity of histopathological examination of the hysterectomy specimen for a definitive diagnosis, the different criterion considered in the diagnosis, variance in the number of cross-sections taken from the uterine specimen in different studies and insufficient clinical information provided by the operator to the pathologist [1, 5-9].

The cases included in these studies are often within the postmenopausal or perimenopausal period. The mean age of subjects with adenomyosis has been reported to be between 40 and 60 in many studies [5, 7, 9]. In a study where magnetic resonance imaging was used for infertility, adenomyosis was most commonly observed in women in the second and third decades [10]. In a study where woman underwent hysterectomy following cesarean section, the incidence of adenomyosis was found to be 17% [11].

The prevalence of adenomyosis was found in 103 cases (36.4%) out of 298 in this study. With preoperative diagnostic methods such as magnetic resonance imaging becoming further developed and widely used as alternatives to histopathological examination of the uterus, definitive incidence of adenomyosis for all age groups could be determined.

Adenomyosis can be associated with gynecological conditions, such as leiomyoma, endometrial hyperplasia, endometrial carcinoma and endometrial polyps because of the effect of estrogen on the etiology of adenomyosis [1, 5, 7, 8, 12-15]. Similarly in the study group, pure adenomyosis was observed in only 24.27% (25) of cases, while the most common histopathologic findings accompanying adenomyosis were myoma uteri 50.48% (52), endometrial hyperplasia 8.74% (9), endometrial cancer 4.85% (5), endometriosis 2.91% (3) and endometrial polyps 1.9% (2). Although adenomyosis is generally observed in gynecological conditions such as leiomyoma and endometrial hyperplasia, which are known to be associated with high levels of estrogen, it is rarely seen together with endometriosis. This finding supports the idea that they are two distinct pathologies [6, 7, 16]. In this study there was also no significant difference of prevalence of endometriosis in either group.

There are numerous studies where physiological conditions that occur under the effects of estrogen, such as menarche, menstrual cycle and menopause, and bleeding disorders are evaluated in subjects with adenomyosis [17]. However, contradictory results have been reported in these studies. It was reported in one study that there is no relationship between adenomyosis and menstrual cycle pattern, age at menarche and menopause [5], while a strong correlation between adenomyosis and age of menarche, menstrual irregularities and dysmenorrhea was reported in another study [7]. In the present study the mean duration of total reproductive period in subjects with adenomyosis was significantly higher than those in the control group. Although duration of the reproductive period might be influenced by conditions such as obesity, medications and pregnancy, it is a parameter that shows the whole period where the hormonal effects under suspicion in etiology do exist.

It has also been reported that 35% of subjects with adenomyosis have no symptoms [1]. The most commonly observed findings, which are termed as the adenomyosis triad, consist of menorrhagia (50%), dysmenorrhea (30%), and a sensitive, symmetrically expanded uterus. Other less commonly seen symptoms are dyspareunia and chronic pelvic pain. These symptoms are non-specific and are also seen in gynecological conditions that may be associated with adenomyosis [1].

In the present study, the most commonly observed symptoms in subjects with adenomyosis were menometrorrhagia, chronic pelvic pain, dysmenorrhea and dyspareunia. All symptoms were more commonly observed in subjects with adenomyosis, when compared with those in the control group. Nevertheless, in comparison with the control group, pelvic pain, dysmenorrhea and dyspareunia were significantly more common symptoms observed in the study group.

In accordance with the higher rates of menometrorrhagia in the study group, patients with adenomyosis were found to be significantly more anemic and required more blood transfusions than those in the control group.

It has been reported that the uterus could reach a weight of 80-200 g in women with adenomyosis [1]. In some studies where the uterus weight was evaluated together with symptoms and histopathological findings, uterus specimens in subjects only with adenomyosis were found to be significantly lighter than those in subjects with leiomyoma [18, 19]. In this study, mean weight of the uterus of the study group was insignificantly lighter than the control group. In subjects with pure adenomyosis, mean weight of the uterus was 153.09 g. This finding, which is in accordance with the studies in the literature, especially appears to be the result of uterine myoma as an associated gynecological condition.

Many studies have reported that adenomyosis is more frequently seen in multiparous women [5, 7-9]. It was also reported that aggressive trophoblastic activity during pregnancy could lead to an increase in adenomyosis foci within the myometrium, and this could also be predisposed by hormonal status during pregnancy [5]. However,

in contrast to the literature, the rate of nulliparous subjects in our study group was found to be significantly higher when compared with the control group. According to the results of this study, adenomyosis was not predisposed by multiparity, and no significant differences were observed between number of parturitions and adenomyosis.

It has been shown that the estrogen levels were lower in smokers, and accordingly adenomyosis is less commonly seen in smokers. The risks of uterine myoma and endometrial cancer were also lower in smokers, due to decreased levels of estrogen [5]. However, the rate of smoking was observed to be significantly higher in our study group. Although there are many studies on risk factors in the development of adenomyosis, the number of studies in which the relationship between smoking and adenomyosis has been investigated are not adequate. It was reported that the rate of smoking among females has increased in recent years [20]. There is no evidence on a decreased prevalence of adenomyosis or the prevalence of disorders such as leiomyoma or endometrial cancer. Further studies with a higher number of subjects are needed on this issue.

A previous history of uterine surgery, such as early pregnancy termination or cesarean section, is suggested to cause iatrogenically weakness within the endomyometrial junction, leading to invasion of endometrial glands and stroma in the myometrium [6, 7, 21]. There is also another study where such interferences were shown not to cause the development of adenomyosis [5]. In the present study, the rate of subjects with a previous history of uterine surgery (early pregnancy termination, cesarean section) in the study group was found to be significantly higher than those in the control group.

The endomyometrial junction is necessary for sperm transportation, embryonal implantation, placental development and menstruation [22]. Adenomyosis is suggested to cause weakness in the endomyometrial junction due to congenital or acquired factors [14, 15, 23], and might have a relationship with early abortions and infertility. Increased levels of nitric oxide have also been found in adenomyosis, having a negative effect on embryonal implantation and the spermatozoon [24, 25].

Currently, considerable advancements have been achieved in infertility and age of first pregnancy has increased; adenomyosis can be diagnosed during the investigations related to infertility. Adenomyosis has been diagnosed by using magnetic resonance imaging in 14 (53.8%) of 26 patients who were being examined for infertility, menorrhagia and dysmenorrhea [22]. The subjects evaluated in this study were often multiparous patients in their fourth or fifth decades. When the infertility and early abortion histories of the subjects were investigated, no significant differences were observed between the study and control groups. However, subjects with a history of infertility or early abortion were rather few in number.

The relationship between adenomyosis and the conditions under discussion could be further clarified with

higher numbers of subjects included in studies, and with increased use of diagnostic methods during the investigation of the etiology of early abortion and infertility or pelvic pain and dysmenorrhea, such as high resolution sonography and magnetic resonance imaging [26].

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