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## Adenomyosis: Pathologies associated in a set of patients underwent hysterectomy

Luis Humberto Sordia–Hernandez<sup>1\*</sup>, Julio Herrero<sup>2</sup>, Arturo Morales Martinez<sup>1</sup>, Jose María Gris<sup>2</sup>, Donato Saldivar Rodriguez<sup>1</sup>, Oscar Vidal Gutierrez<sup>1</sup>, Celina Castro<sup>1</sup>

<sup>1</sup>University Center of Reproductive Medicine, University Hospital, “Dr. José Eleuterio González, Autonomous University of Nuevo León”, Monterrey, México

<sup>2</sup>Servicio de Ginecología Hospital Vall d’Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain

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### ABSTRACT

**Objective:** To determine if a relationship exists between the histopathological diagnosis of adenomyosis and the clinical conditions and pathologies that are more commonly related to it in patients undergoing hysterectomy. **Methods:** Retrospective, comparative, case–control study was conducted. With previous approval by ethics committee, we included 794 patients undergoing hysterectomy at a University Hospital. The Medical records and pathology reports of patients undergoing hysterectomy over a two–year period were reviewed. Clinical conditions and associated pathologies, in patients with and without adenomyosis, were reviewed and compared. Statistical analysis was done using the Chi–square test. **Results:** Adenomyosis was reported in 140 out of 794 patients, 17.6% (95% CI: 15.1–20.4). No differences in adenomyosis prevalence were found among patients with or without uterine fibroids, 20.2% (75/371) vs. 15.5% (65/423); endometrial polyps, 9.7% (6/62) vs. 18.3% (134/732); and the presence or lack of endometrial hyperplasia 13.9% (5/36) vs. 17.4% (135/758). The prevalence of adenomyosis among patients with endometriosis was 40.7% (11/27), and among those without this diagnosis, 16.8% (129/767). This difference was significant ( $P=0.001$ ). A history of two or more curettages was also positively related to adenomyosis. **Conclusions:** There was a statistically significant difference in the prevalence of adenomyosis in women with endometriosis when compared to women without endometriosis. A higher incidence of adenomyosis was found in patients with a history of two or more curettages. Trauma to the endometrium could explain the higher incidence of adenomyosis in both conditions.

## 1. Introduction

Adenomyosis is a benign pathology defined as the presence of endometrial glands and stroma within the myometrium surrounded by hyperplastic and hypertrophic myometrium, which produces growth of the uterus[1]. The etiology of adenomyosis is controversial due to the fact

that its prevalence has not been precisely defined and its natural history has not been clarified. However, it has been accepted that adenomyosis is produced by invasion of endometrial glands and stroma in the myometrium[2,3].

The prevalence of adenomyosis reported in the literature varies from 5% to 70%[2]. Adenomyosis is more common in multiparous women. Parity seems to be positively related with adenomyosis[4]. It is also more common among women in the final stage of their reproductive life[5].

Approximately one third of adenomyosis cases are asymptomatic. The symptoms related to adenomyosis are totally nonspecific. In symptomatic cases, abnormal bleeding, pelvic pain, uterine growth and other symptoms can be found[6].

The diagnosis of adenomyosis is rarely made

\*Corresponding author: Luis Humberto Sordia–Hernandez, M.D., Ph.D., University Center of Reproductive Medicine, University Hospital, “Dr. José Eleuterio González, Autonomous University of Nuevo León”, Monterrey, México. Av. Madero y Gonzalitos, Colonia Mitras Centro, Monterrey Nuevo León, 64460, Mexico.

Tel/Fax: +52 (81) 83 48 30 54

E–mail: lsordia@prodigy.net.mx

preoperatively; however, recently, magnetic resonance image (MRI) and 3D ultrasound have increased the possibility of reaching a preoperative diagnosis of adenomyosis[7]. Some pathologies, such as uterine fibroids, endometrial hyperplasia, endometrial polyps and endometriosis among others had been inconsistently related with the presence of adenomyosis[1,8-10].

The aim of this study was to determine if a relationship exists between the histopathologic diagnosis of adenomyosis and the clinical conditions most commonly related to it in patients undergoing hysterectomy.

## 2. Material and methods

This was a retrospective, comparative, case-control study performed at the Universidad Autónoma de Nuevo León University Hospital in Monterrey, Mexico between January 1, 2010 and December 31, 2011. With prior authorization from the Ethics Committee of the institution, surgical reports of hysterectomies performed between 2007 and 2009 were reviewed. Patients were contacted by telephone, e-mail, or telegram to ask for their consent to participate in this study.

During this period, 1 121 patients underwent hysterectomy. Of these 917 contacts were achieved, and 96 refused to participate in the study. A complete file was not found in 27 patients. The final study group included 794 patients, with 140 diagnosed with adenomyosis, which integrated the study group, and 654 without a diagnosis of adenomyosis, which integrated the control group.

Age at the time of hysterectomy, preoperative diagnosis, menstrual history (duration, dysmenorrhea, and whether it was mild, moderate, or severe), number of pregnancies, caesarean sections and abortions, were reviewed. The pathology report was reviewed to document the presence of adenomyosis as well as associated pathologies (uterine fibroids, endometriosis, endometrial hyperplasia and endometrial polyps). A comparison of the findings in both groups was made.

Statistical analysis was using the Chi-square test with SPSS 16.0 statistics software for Mac.

## 3. Results

A diagnosis of adenomyosis was reported in 140 of 794 patients, which corresponded to 17.6% (95% CI: 15.1-20.4). Average age at the time of hysterectomy was 43.0 years in patients with adenomyosis, and 44.1 years in patients without this diagnosis.

Preoperative diagnoses were similar in patients with and without a diagnosis of adenomyosis. No significant statistical difference was found. The most common diagnoses in the adenomyosis group were abnormal uterine bleeding 46.4% (65/140), uterine fibroids 37.1% (52/140), and pelvic relaxation 8.6% (12/140). In the group of patients without adenomyosis, the most common preoperative diagnoses were abnormal uterine bleeding 44% (284/654), uterine fibroids 28.6% (187/654), and pelvic relaxation 18% (118/654). Other less common preoperative diagnoses in both groups were high and low grade squamous intraepithelial lesions, cervical cancer, endometrial hyperplasia, severe pelvic

inflammatory disease, and adnexal tumors either benign or malignant. It must be pointed out that a preoperative diagnosis of adenomyosis was not made in any case.

According to age, the prevalence of adenomyosis among patients under 30 years was one out of 27 patients (0.7%); in patients 31 to 40 years of age 49/272 (18.0%); in patients 41 to 50 years of age 80/382 (20.9%); in those 51 to 60 years 6/56 (10.7%). Meanwhile in patients older than 61 years, it occurred in 4/57 (6.6%). The difference between age groups was statistically significant ( $P=0.007$ ) (Table 1).

Among 448 patients denying a history of dysmenorrhea, a prevalence of adenomyosis of 18.5% (83/448) was found. Among those with mild dysmenorrhea it was 16.9% (47/278). In those with moderate dysmenorrhea it was 12.7% (6/47) and in patients with severe dysmenorrhea it was 19.0% (4/21). The difference between the groups was not statistically significant ( $P=0.959$ ) (Table 2).

According to the number of pregnancies, we found that 49 patients were nulligravidas with a prevalence of adenomyosis of 20.4% (10/49). Among patients with one or two pregnancies the prevalence was 13.3% (22/168) and among those with three or more pregnancies, 18.7% (108/577)  $P=0.211$  (Table 3).

According to the number of deliveries, it was found that in nulliparous patients a prevalence of adenomyosis of 18.6% (34/183) was reported. Among patients with one or two deliveries it was 16.6% (34/205), and in patients with three or more deliveries 17.7% (72/406)  $P=0.873$  (Table 3).

A prevalence of adenomyosis of 17.1% (91/531) was found among patients without a caesarean section. In patients with one or two caesarean sections it was 19.6% (33/168), and among patients with three or more previous caesarean sections it was 16.8% (16/95),  $P=0.746$  (Table 3)

The prevalence of adenomyosis was 16.5% (105/636) among patients without a history of abortion; of 21.6% (33/153) among those with one or two abortions, and of 40% (2/5) among patients with three or more abortions,  $P=0.144$  (Table 3)

A prevalence of adenomyosis of 17.2% (124/720) was found among patients without a history of curettages; of 13.2% (7/53) among those with one curettage; 43.0% (7/16) among those with two curettage and 40% (2/5) among patients with three curettages (Table 3) with a statistically significant difference ( $P<0.01$ )

When abortions were treated by manual vacuum aspiration (MVA), a prevalence of adenomyosis of 17.4% (124/713) was found among patients without a history of MVA; among those with one MVA 19.7% (13/66); and of 20.0% (3/15) among those with two MVA,  $P=0.86$ , (Table 3).

A total of 371 patients were reported to have uterine fibroids regardless of whether it were intramural, subserosal, or submucous. Among these, 20.2% (75/371) had a diagnosis of adenomyosis; however, among patients without uterine fibroids the prevalence of adenomyosis was 15.5% (65/423).

The prevalence of adenomyosis was 18.8% (59/314) and 16.9% (81/480) among patients with and without a diagnosis of intramural uterine fibroids, respectively. Among patients with a diagnosis of submucosal uterine fibroids it was 24.1% (7/29), meanwhile among patients without this diagnosis it was 17.3% (133/765). Among patients with and without endometrial hyperplasia, the prevalence of adenomyosis was

13.9% (5/36) and 17.4% (135/758), respectively. In the case of patients with or without endometrial polyps, adenomyosis was present in 9.7% (6/62) and 18.3% (134/732) of the cases, respectively. No statistically significant differences were established between any of the previously mentioned variables (Table 4).

On the other hand, the prevalence of adenomyosis among patients with endometriosis was 40.7% (11/27), and among those without this diagnosis it was only 16.8% (129/767). This difference was highly significant ( $P=0.001$ ) (Table 4).

**Table 1**

Age groups and adenomyosis.

Age group	Frequency	Percentage (%)
Less than 30 years	1/27	0.7
31 to 40 years	49/272	18.0
41 to 50 years	80/382	21.3
51 to 60 years	6/56	10.7
Greater than 60 years	4/57	6.6

 $P=0.007$ .**Table 2**

Adenomyosis and dysmenorrhea.

Dysmenorrhea	Frequency	Percentage (%)
Without dysmenorrhea	83/448	18.5
Mild dysmenorrhea	47/278	16.9
Moderate dysmenorrhea	6/47	12.7
Severe dysmenorrhea	4/21	19.0

 $P=0.959$ .**Table 3**

Adenomyosis and obstetrical history.

Obstetrical history	Frequency	Percentage (%)
Pregnancies <sup>a</sup>		
Without pregnancy	10/49	20.4
One to two pregnancies	22/168	13.1
More than three pregnancies	108/577	18.7
Deliveries <sup>b</sup>		
Without deliveries	34/183	18.6
One to two deliveries	34/205	16.6
Three or more deliveries	72/406	17.7
Cesarean sections <sup>c</sup>		
Without cesarean section	91/531	17.1
One to two cesarean sections	33/168	19.6
Three or more cesarean sections	16/95	16.8
Abortions <sup>d</sup>		
Without abortions	105/636	16.5
One or two abortions	33/153	21.6
Three or more abortions	2/5	40.0
Curettage history <sup>e</sup>		
Without curettage	124/720	17.2
One curettage	7/53	13.2
Two curettages	7/16	43.0
Three curettages	2/5	40.0
Manual vacuum aspiration (MVA) history <sup>f</sup>		
Without MVA	124/713	17.4
One MVA	13/66	19.7
Two MVA	3/15	20.0

<sup>a</sup> $P=0.211$ ; <sup>b</sup> $P=0.873$ ; <sup>c</sup> $P=0.746$ ; <sup>d</sup> $P=0.144$ ; <sup>e</sup> $P<0.01$ ; <sup>f</sup> $P=0.86$ .**Table 4**

Adenomyosis and associated pathologies.

Pathology	With adenomyosis	Without adenomyosis	<i>P</i>
Uterine myomatosis	75/371 (20.2%)	65/423 (15.5%)	0.074
Intramural myomas	59/314 (18.8%)	81/480 (16.9%)	0.489
Submucosal myomas	7/29 (24.1%)	133/765 (17.3%)	0.349
Endometrium hyperplasia	5/36 (13.9%)	135/758 (17.4%)	0.546
Endometrial polyp	6/62 (9.7%)	134/732 (18.3%)	0.087
Endometriosis	11/27 (40.7%)	129/767 (16.8%)	0.001*

\*Statistically significant.

## 4. Discussion

In this study, a prevalence of adenomyosis of 17.6% was found in a group of patients subjected to hysterectomy, whether abdominal or vaginal, independently of the benign or malignant nature of the surgical indication for hysterectomy. This prevalence is found within the wide range previously reported in the literature for this disorder<sup>[2]</sup>; however, it varies considerably due to different factors. It is undoubtable that the frequency with which this pathology is reported is greatly influenced by the diagnostic criteria used to define it. Most criteria take into account the distance between the endometrial–myometrial interface and the endometrial glands that invade the myometrium. Traditionally, this distance has been established as 4 mm<sup>[11]</sup>; however, less strict criteria that consider the invasion of even a distance less than 2 mm to establish the diagnosis have been described<sup>[1,12]</sup>. This difference between criteria reflects on the amount of times the diagnosis of adenomyosis is found in pathology reports. A universally accepted algorithm to standardize diagnostic criteria for adenomyosis does not yet exist. Maybe the most solid proposal to date is that of Vercellini *et al.* in 2006<sup>[13]</sup>. They propose a system that considers the presence of adenomyosis, the depth of invasion, the extent of spread, and the configuration of the lesion, namely focal or diffuse. This evaluation of adenomyosis could result in at least a uniform way of describing this pathology.

In this study no relationship was demonstrated between the prevalence of adenomyosis and a history of dysmenorrhea, whether mild, moderate, or severe, and a history of chronic pelvic pain. All this can be explained by the fact that these symptoms have been related in an inconsistent way to the diagnosis of adenomyosis<sup>[14]</sup>.

Adenomyosis is more prevalent at the final stage of a woman's reproductive life, mainly between 35 and 50 years of age<sup>[8]</sup>. In our study, a statistically significant difference between the prevalence of adenomyosis and the age of the patients was found, since more than 50% of the patients with a diagnosis of adenomyosis were between 40 and 50 years of age. This is probably because at this age most patients have already had children, with this being an influent factor; although it must also be considered that such an increase in the prevalence of adenomyosis could be related to estrogen levels that at the end of the woman's reproductive life tend to rise before definitely decreasing after menopause. High estrogen levels have been related to uterine hyperperistalsis, which could be a determining factor in the pathogenesis of adenomyosis, although this has also been related with pelvic endometriosis. However, total estrogen serum levels may not differ between patients with and without adenomyosis<sup>[15]</sup>.

Adenomyosis principally occurs among women who have been pregnant. In our study, 92.8% of patients with a diagnosis of adenomyosis had had at least one pregnancy, with this matching previously reported data<sup>[13,16]</sup>. However, when examining if the prevalence of adenomyosis differed according to the number of pregnancies, no statistically significant difference was identified between patients who had not been pregnant and patients with one, two, three, or more pregnancies. There was also no difference between the number of deliveries, caesarian sections, or abortions.

A good number of pathologies such as uterine fibroids, endometrial hyperplasia, endometrial polyps and endometriosis among others have been inconsistently related with the presence of adenomyosis<sup>[1,8–10]</sup>. In this study, the prevalence of adenomyosis in patients with uterine fibroids (independently of its localization) or without this pathology, was not significantly different. It was also not possible to demonstrate any difference in the prevalence of adenomyosis among patients with exclusively intramural or sub mucosal fibroids.

The prevalence of adenomyosis in patients with endometrial pathology, whether benign or malignant, has been widely described<sup>[1,10]</sup>. In this study a greater incidence of adenomyosis was not found among patients with a pathology report of endometrial hyperplasia or endometrial polyp.

Probably, the pathology that has been more convincingly related to adenomyosis is endometriosis<sup>[2,9,17]</sup>. These results match those found in this study, since a highly significant relationship between both pathologies was established, where the incidence of adenomyosis was 40.7% among women with endometriosis. Leyendecker *et al.* previously suggested a dysfunction in the junction zone or archimeta as a possible pathologic factor in both adenomyosis and endometriosis<sup>[18]</sup>. This may be related to the hyperperistalsis local as a pathogenic factor. As previously stated focal hyperperistalsis may be related to a myometrium invasion by endometrial glands and stroma in patients with adenomyosis, and also may be associated to a possible migration of this to the peritoneal cavity in patients with endometriosis. This may represent the common pathogenic factor between these pathologies.

Uterine fibroids were the most frequent pathology associated with adenomyosis. However, prevalence of adenomyosis was similar in patients with and without uterine fibroids. Although endometriosis was not the pathology more commonly seen in women with adenomyosis, there was a statistically significant difference in adenomyosis prevalence when we compared women with and without endometriosis. So we can conclude that a positive association in endometriosis and adenomyosis may exist. Perhaps, we need studies involving more patients to effectively prove this association. As well, since a higher incidence of adenomyosis was found in patients with history of two curettages, trauma to the endometrium may explain the higher incidence of adenomyosis in both, endometriosis and curettages. Age and parity also correlated with a high incidence of adenomyosis, as previously had been reported. If adenomyosis is a true disease with its own symptomatology or only a relative frequent anatomo–pathology diagnosis is still a question of discussion.

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## Conflict of interest statement

All the authors of this manuscript certify that no competing financial interests exist.

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