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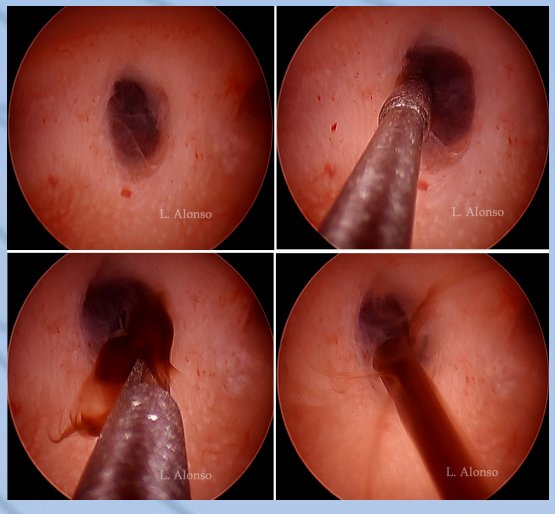


HYSTEROSCOPY Editorial teaM

Dear hysteroscopy friends,

Another year has come and gone, I am not sure if I prefer to look back at a crazy year that just past or to look forward to a 2022 that is starting to post a big challenge ahead of us, another Coronavirus variant "Omicron" that now wants to combine with the well known Flu virus and create the "Flurona". However, our hysteroscopy Newsletter is ready to face any challenge that will come at us and is now starting its 8th year since its creation, and how a better way to start this year than with a comprehensive issue dedicated to a complex and enigmatic condition "Adenomyosis".

This new issue of our Newsletter, that you now have in from of you, start with a very interesting article, in which Dr Luis Alonso, once again, provide us with a comprehensive review of the pathology along with images that, as always, have such a high quality, that you will feel like reading an issue of the "National Geographic" magazine. In a very, easy to understand way, he will take you from history of the disease, pathogenesis, will describe the different types of adenomyosis, to then review its clinical course, diagnosis, and treatment. Following Dr Alonso's article, a well recognized group from the Hospital Universitario "12 de Octubre" from Madrid, dives deep into the role of ultrasound in the diagnosis of adenomyosis. You will be immersed into deep water, learning about embryology, etiology theories and different phenotypes that make adenomyosis such an interesting disease. At the end of their article, they will then provide you a "template" of the ideal ultrasound report, highlighting important aspects that must be included in the ultrasound report to help the clinician treating the patient with adenomyosis.

Then, our passion, hysteroscopy and its role in patients with adenomyosis is presented in a very elegant way by Attilio (no need to write his last name, since everyone knows that there is no other Attilio in the word of hysteroscopy, than Professor Di Spiezio Sardo) and Dr Virginia Foreste, their images and the simplified hysteroscopic approach, in both office setting and the operating room, will provide you all the tools you need to understand the value and limitations that hysteroscopy has in this clinical condition.

A very interesting type of adenomyosis is the "Cystic adenomyosis" in which case hysteroscopy could play an important therapeutic role, is presented by our dear friend Alejandro Gonzalez et al. from Hospital Naval in Buenos Aires, Argentina.

This extremely interesting and comprehensive issue of hysteroscopy Newsletter concludes with 3 important aspects of adenomyosis which are the non-surgical treatment (presented by Dr Mykhailo Medvediev, Ukraine) the role of endometrial ablation (Dr Thiago Guazzelli, Sao Paulo, Brazil) and its impact on fertility (Dr Elena Puente, Málaga, Spain)

Looking forward to a very challenging and interesting year that we have ahead of us and with the energy and commitment that the Hysteroscopy Newsletter team has always had, I leave you with the first issue of year Number 8th of Hysterosocpy Newsletter.

Cheers,

Jose "Tony" Carugno
University of Miami. USA

If you are interested in sharing your cases or have a hysteroscopy image that you consider unique and want to share, send it to hysteronews@gmail.com

Adenomyosis: A Review

Luis Alonso Pacheco

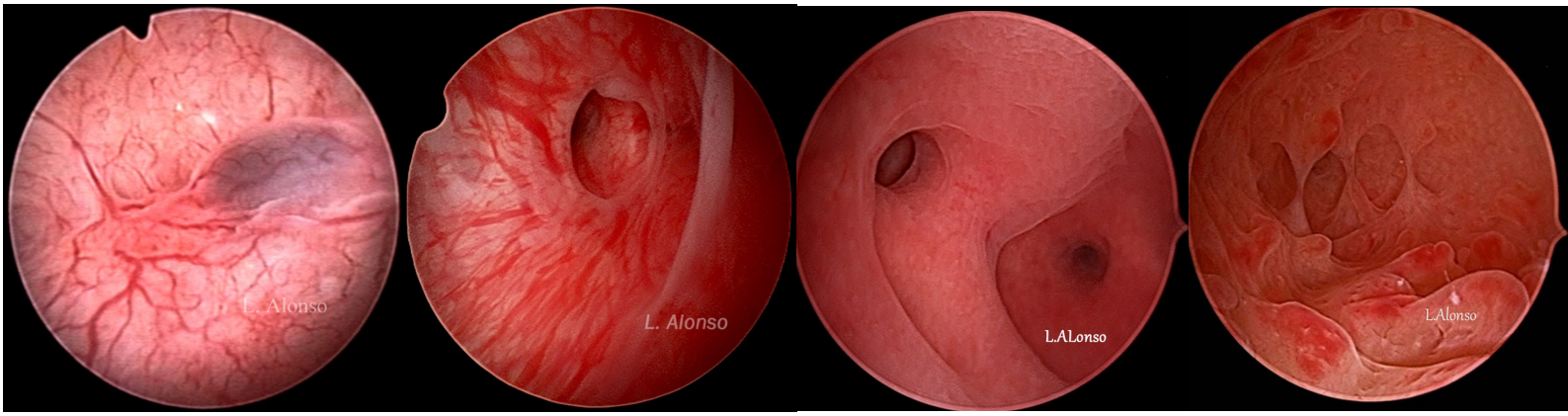
Centro Gutenberg. Málaga. Spain

Hysteroscopy Newsletter Vol 8 Issue 1

INTRODUCTION

Adenomyosis is defined as the presence of ectopic endometrial tissue inside the myometrium. This accumulation of endometrial glands and stroma in the myometrium causes hypertrophy of the surrounding myometrium.

It was described for the first time by Rockitansky in 1860 when observing the existence of glands and endometrial cells inside the myometrium and which he called “adenoid uterium cystosarcoma” (1). It was a few years later, in 1925, when Frankl first used the term "adenomyosis" and described the presence of direct communication between the endometrial islets located in the myometrial thickness and the endometrium (2). Finally in 1972 Bird more clearly defined adenomyosis as a “benign invasion of the myometrium by the endometrium” (1)



PATHOGENESIS

Various theories have been proposed as to the origin of adenomyosis, however the true cause remains unknown. The most widely accepted theory is that adenomyosis occurs as a consequence of tissue trauma that, after a poor repair process favors invagination of the endometrium on the injured tissue (3). Another theory supports that adenomyosis is the consequence of a process of metaplasia on remaining pluripotent cells of the Müllerian ducts.

Although the true origin remains unknown, certain risk factors associated with the development of this pathology are known. Several studies have found an association between the number of pregnancies and the presence of adenomyosis, with a greater trend in those patients with a history of abortion (4).

Although adenomyosis can also appear in young patients, there appears to be an increased risk in older patients. Other known risk factors include previous uterine surgery or tamoxifen treatment.

TYPES

There is still no consensus on the depth that endometrial penetration must reach to define it as adenomyosis, although the most accepted cut-off point is 2.5mm below the myometrial endometrial junction. It is important to remember at this point that the endometrium rests directly on the

myometrium at the level of the endometrial-myometrial junction or junctional zone (JZ), with an absence of mucous basement membrane.

Adenomyosis is divided into several types

***Focal*:**

Adenomyosis affects a certain area of the myometrium and can resemble a myoma, hence the term "adenomyoma". Obviously, this adenomyoma does not have a pseudocapsule that separates it from the healthy myometrium and the vascularization is diffuse throughout the lesion and not peripheral as in the case of fibroids.

Diffuse:

Affecting the entire uterine wall and causing an increase in the size and volume of it or even the entire uterus. This diffuse adenomyosis tends to affect the posterior uterine wall more frequently, then less frequently the anterior wall and rarely the coronal areas or areas close to the cervix (1)

Cystic:

The term cystic adenomyosis is reserved for those cases, focal or diffuse, in which cysts with blood content greater than 1 cm in diameter are appreciated. There is a variant that is "juvenile cystic adenomyosis" that affects young women under 30 years of age in whom the adenomyosis cyst cause severe dysmenorrhea

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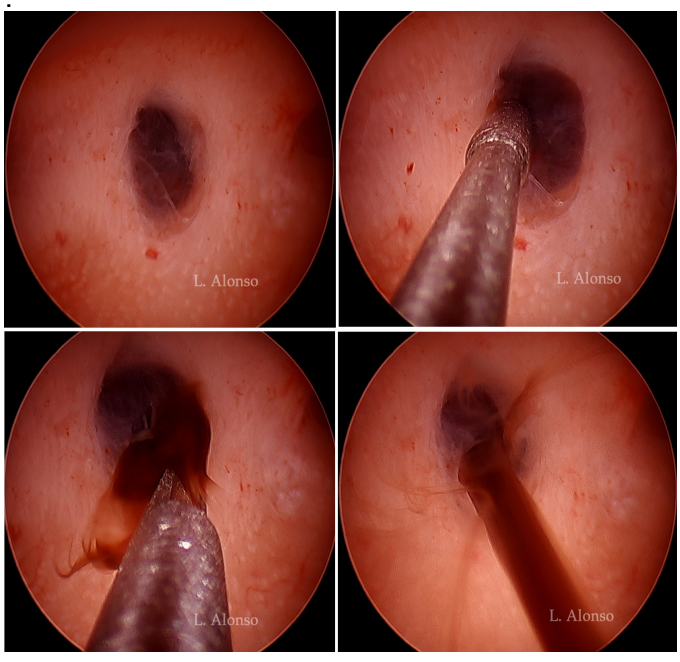


PREVALENCE

It is difficult to estimate the true prevalence due to the lack of well established diagnostic criteria as well as the bias that occurred years ago when studying only hysterectomy specimens and therefore in an older population.

Based on hysterectomy specimens the prevalence varies between 20-30%, although there is great variation between the different studies, with the data varying between 5-70%. Different studies based on imaging techniques established an approximate incidence of between 20-30% (5).

Of all cases of adenomyosis, approximately 30% affect women under 30 years of age, so we can say that this pathology can affect women throughout their reproductive life

CLINICAL COURSE

Patients with adenomyosis have different symptoms, including dysmenorrhea, abnormal uterine bleeding, and infertility. Not all women with adenomyosis are symptomatic and the intensity of symptoms varies according to the type and extent of adenomyosis

Abnormal uterine bleeding:

It is the most frequent symptom and can affect up to 50% of patients. The presence of hypervascular areas, an increase in the endometrial surface derived from the increase in uterine size, together with dysfunctional contractility seem to be the causes of this symptom.

***Dysmenorrhea**:*

Affects approximately 30% of patients. Different theories have been proposed to explain why adenomyosis causes dysmenorrhea, it seems that the existence of uterine hypercontractility together with an increase in menstrual flow may be the triggering factors. It should be remembered that endometriosis coexists with endometrial adenomyosis in up to 24% of cases, and endometriosis may also contribute to dysmenorrhea.

Infertility:

Although classically no attention has been

paid because it was diagnosed mainly in multiparous women, the existence of a direct relationship between adenomyosis and infertility has been demonstrated, ruling out the existence of concomitant endometriosis (6). The cause of this association remains unknown, although it could be due to abnormal uterine peristalsis as well as associated immunological changes. We should also remember the role that associated endometriosis can play in patients with infertility.

Chronic pelvic pain and dyspareunia:

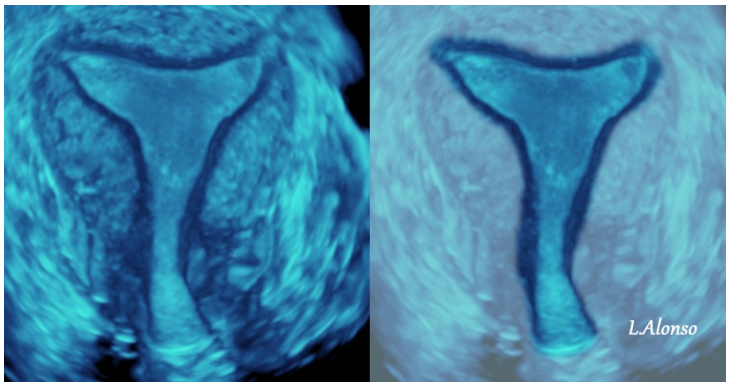
These are less common symptoms.

DIAGNOSIS

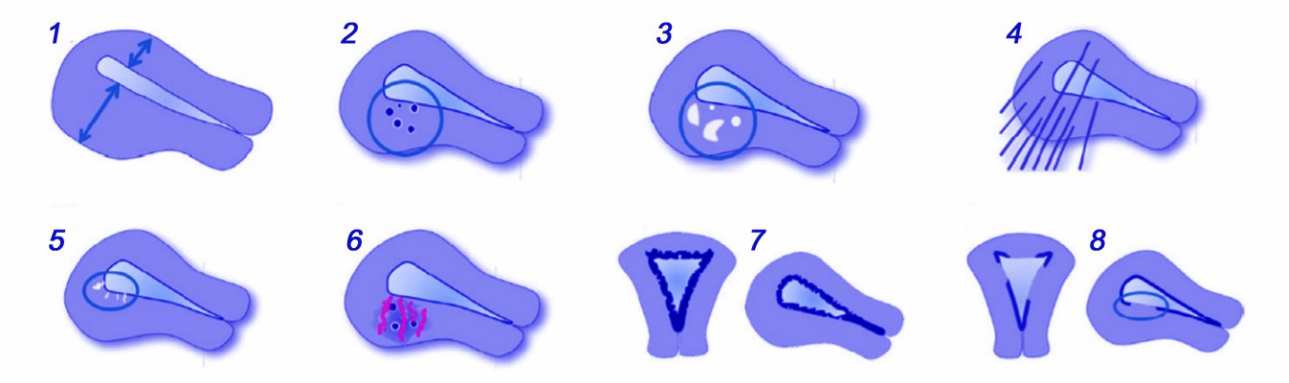
The diagnosis of this pathology is based on the medical history and the gynecological exam. But today imaging studies play a capital role in diagnosis, establishing the definitive diagnosis with histopathological confirmation.

1- ***2D Ultrasound:*** The different ultrasound patterns suggestive of adenomyosis were established in a consensus document by the MUSA group (Morphological Uterus Sonographic Assessment) and consist of the following:
A. Asymmetric thickening of the uterine walls
B. Presence of cysts in the myometrial thickness, hypoechogenic islets, shadowing, sub-endometrial echogenic lines and stippling
C. Translesional vascularization, irregular endometrial-myometrial transition and interrupted endometrial-myometrial transition. The accuracy of the diagnosis with these criteria is greater than 90%. Asymmetric thickening, sub-endometrial hyperechogenic lines, and interruption of the endometrial-myometrial transition seem to be the most accurate markers for diagnosis by 2D ultrasound (7).

2-*3D Ultrasound:* 3D Ultrasound allows obtaining a coronal plane in which the endometrial / myometrial interface can be observed with detail, also called junctional zone (JZ), which appears as a hypoechoic area surrounding the endometrial cavity. It has been noted that an irregular junctional zone with increased thickness constitutes a high precision ultrasound criterion for the diagnosis of adenomyosis.



3- ***Nuclear Magnetic Resonance Imaging (MRI):*** For years it has been considered the most accurate technique in the diagnosis of adenomyosis although today, many authors consider its diagnostic precision similar to that of 3D ultrasound (8). The main diagnostic criterion is the presence of endometrial foci in the thickness of the myometrium. This sign is considered pathognomonic although it only appears in 50% of cases. Other indirect signs are the presence of hyperintense linear striations that run from the basal to the myometrial thickness, thickening of the Junctional zone greater than 12mm, visualization of a globular and enlarged uterus and poor definition of the junctional zone with irregular areas.



4- *Hysteroscopy:* Hysteroscopy is considered the gold standard for the diagnosis of intracavitary pathology. Although adenomyosis affects the myometrium and not the endometrium, there are a series of hysteroscopic patterns highly suggestive of adenomyosis, such as the existence of irregular endometrium with surface defects, the existence of hemorrhagic cystic lesions with dark blood inside, and the existence of fibrous-looking areas (9). Hysteroscopy also allows obtaining biopsies that facilitate the establishment of a definitive diagnosis.

TREATMENT

Although traditionally the treatment of patients with adenomyosis and associated symptoms has been hysterectomy, in recent years this trend has changed and more conservative treatments are often performed. This has happened for two main reasons, on the one hand the efficacy of different medical treatments in improving the symptoms of patients with adenomyosis, and on the other hand, thanks to imaging techniques it has been observed that this pathology also affects young patients with desire to preserve future fertility in which hysterectomy cannot be considered as a viable form of treatment.

Hormonal treatments include both combined oral contraceptives such as the levonorgestrel-releasing IUD or continuous progestin treatment (OCP). Both act on the endometrium producing a decrease in menstrual bleeding and an improvement in pain. A randomized study that compared the efficacy of both, found that LNG-IUD produced a greater decrease in pain and bleeding than OCP. Continuous progesterone induces a decidualization of the endometrium along with endometrial atrophy. Improving the symptomatology of these patients.

The use of GnRH analogs is temporary option. These analogs induce suppression of ovarian function and therefore induce an hypoestrogenic state. The use of GnRH analogs is more frequent in patients who undergo assisted reproductive technique in which a decrease in the activity of adenomyosis is required since the use of analogs suppresses the inflammatory reaction in the tissues and angiogenesis, therefore decreasing the degree of adenomyosis activity.

Other non-surgical options include uterine artery embolization, which has been shown to be effective in patients with abnormal uterine bleeding and dysmenorrhea (10). Ultrasound-guided or resonance-guided ultrasound ablation with similar rates of efficacy and the use of radiofrequency ultrasound. The three techniques pursue the destruction of the adenomyoma tissue, thus improving the symptoms.

Conservative surgical techniques include effective hysteroscopic drainage of adenomyosis cysts, especially improving associated dysmenorrhea, effective endometrial ablation or resection for the treatment of abnormal uterine bleeding, and cytoreductive surgery for focal adenomyosis, which is a complex surgery with promising results only in expert hands.

CONCLUSION

Adenomyosis is an enigmatic condition both in its origin and in its treatment. The management of this pathology depends above all on the desire of future fertility of the patients. Today, the most conservative treatments are those that should be used as the first option, reserving surgical techniques as second line alternatives.

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Sonographic diagnosis of adenomyosis

José Manuel Puente. Gregorio López. Alberto Galindo

Hospital Universitario "12 de Octubre" Madrid. Spain

INTRODUCTION

Adenomyosis is defined by the presence of endometrial tissue (glandular and stroma) inside the myometrium, therefore outside its usual location, the uterine cavity. This endometrial tissue presence causes hypertrophy and hyperplasia of the surrounding myometrium.

Adenomyosis remains today a complex disorder, difficult to assess. This is contributed by the fact that there are no uniformly accepted histological or radiological criteria.

The diagnosis of adenomyosis is made based on pathology. However, and given its association with infertility and the possibility of carrying out medical treatment of the associated symptoms (dysmenorrhea, hypermenorrhea), the diagnosis or suspicion should be made in most cases by means of an imaging test, ultrasound being the initial diagnostic method and reserving magnetic resonance imaging (MRI) for cases in which there is doubt in the diagnosis (1). This is especially important from the reproductive point of view since adenomyosis is not a problem of the last few years of the reproductive life but also affects young patients who are often associated with endometriosis.

Early and accurate diagnosis of adenomyosis allows adequate treatment and follow-up as well as provide information about its reproductive impact and its correlation with the adverse obstetric prognosis in relation to placentation deficit.

Within ultrasound there are well-defined criteria within the MUSA study group (2), however there is currently no consensus (3) on how many criteria are necessary to establish a reliable diagnosis, with at least two criteria being the recommendation of most experts. Three-dimensional ultrasound, by better assessing the endometrial-myometrial transition zone, can improve diagnostic sensitivity and specificity (4).

Several phenotypes of adenomyosis have been described (5), depending on whether it originates from the endometrium, crossing the endometrial-myometrial transition zone (also known as internal myometrium or junctional zone JZ) or if it is produced by direct invasion from the outside, more commonly associated with endometriosis.

An adequate history helps establishing the ultrasound diagnosis of adenomyosis. The presence of dysmenorrhea, hypermenorrhea or infertility or its frequent association with endometriosis (6,7) means that we must always bear in mind the suspicion of adenomyosis in this context.

Adenomyosis can appear from the early stages of life, and manifest itself after menarche. The best way to understand the natural history of the disease would be to study a large cohort of young patients and monitor the changes that occur throughout their reproductive lives. This study has not been carried out to date and therefore we have to rely on studies on different populations to try to understand the natural evolution of the process.

EMBRIOLOGY

To properly understand the etiology theories of adenomyosis, it is essential to know the embryology, anatomy and myometrial physiology since the uterine myometrium is not homogeneous but has two layers:

1- Internal myometrium (endometrial-subendometrial unit, archimetra, archimometrium, transition zone or "junctional zone"), which comes from the mesonephric or Müllerian ducts formed by bundles of short muscle fibers arranged in a circle. It has estrogen and progesterone receptors and responds to hormonal cyclical variations. Responsible for cyclical peristaltic activity

2- External myometrium, thicker and derived from a non-Mullerian tissue formed by bundles of long longitudinal fibers.

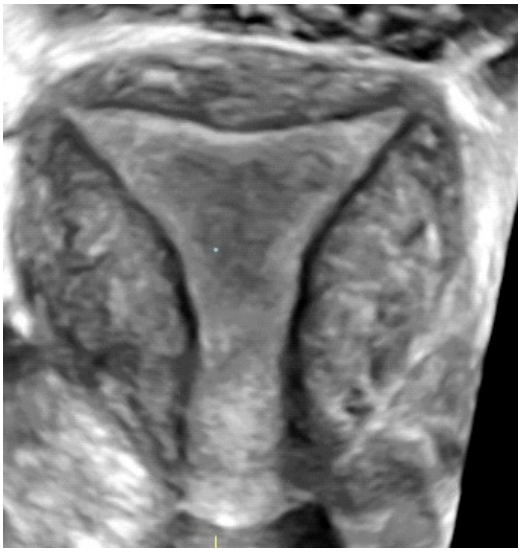

Figure 1. Normal internal myometrium. Three-dimensional (3D) ultrasound, coronal plane Hypoechoic sub-endometrial area (arrow).

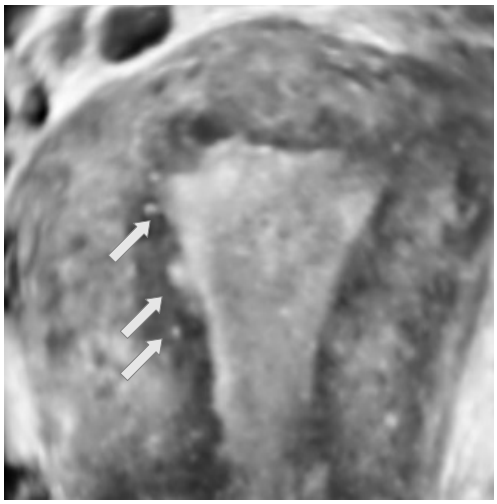

Figure 2. 3D ultrasound showing an irregular internal myometrium covered by hyperechogenic bands originating from the endometrium (arrows)

ETIOLOGY THEORIES

Several "phenotypes" of the disease have been described, possibly associated with the different etiology mechanisms (8) that have been described to explain it, being the most accepted the following two:

1.- Tissue damage and repair due to repeated microtrauma on the endometrial-myometrial transition zone (as sea waves act on coastal rocks) originated by uterine peristalsis, mediated by estrogenic hormonal stimulation during some situations such as abortions, deliveries, curettage, that favors the "herniation" of endometrial cells towards the junctional zone (jz), and from there to the rest of the myometrium (9). It can also be caused by compression of the external myometrium (or neometer) on the internal (archimetric), being more frequent in patients with dysmenorrhea. The absence of a barrier between the endometrium and the myometrium makes it even more vulnerable to these invasions. This highlights the importance of avoiding trauma to the endometrial cavity (ie sharp curettage).

2.- Coelomic metaplasia: metaplastic changes arising from the myometrial Mullerian remnants with the capacity to originate stroma and endometrial glands. Similarly, there are adult stem cells in the uterus that are capable of cyclically regenerating the endometrium. They are found in the basal layer of the endometrium. The phenomenon of retrograde menstruation makes it easier for some of these cells to reach the peritoneal cavity, especially at the level of the cul-de-sac, and from this location they can colonize the surrounding tissues, mainly the posterior uterine surface. We need more evidence to strengthen this hypothesis, but it is a fact that not all cases of adenomyosis can be explained with the theory of damage and repair.

ADENOMYOSIS PHENOTYPES

Based on the aforementioned etiology theories, an "internal" or type I adenomyosis, originating from the endometrium towards the transition junction zone (JZ), another "external" or type II adenomyosis, which would affect the external myometrium (figure) without affecting the jz. There would be a type III in which the intermediate layer of the myometrium would be affected without involvement of JC or serosa and finally a type IV or indeterminate not included in the previous types. A recent study (10) described that women with external adenomyosis were significantly younger, nulliparous and more likely to have associated endometriosis, compared to women in the internal adenomyosis group

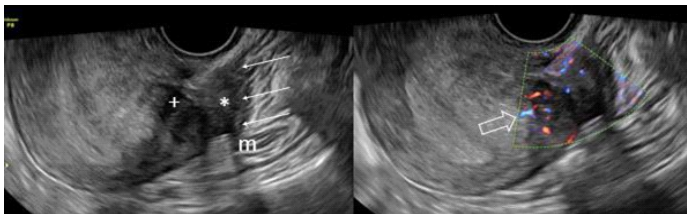

Figure 3.- "External" adenomyosis. Sagittal retroversion of the uterus showing an adenomyotic nodule (+) in close continuity with an endometriotic implant (*) that affects the sigmoid colon. The arrows indicate the area where the normal structure of the muscular layer of the colon is lost (m) and the hollow arrow indicates the typical trans-lesion vascularization of the adenomyoma.

SYSTEMATIC SONOGRAPHIC EVALUATION

The examination should be performed transvaginally, with an empty bladder. On some occasions, we must complement the transabdominal examination in cases of indifferent uterine position or coexistence of endometriosis or fibroids, which could hinder adequate uterine sonographic evaluation through the transvaginal route. In cases of suspected external adenomyosis, an expanded examination in 4 steps proposed by the IDEA group (International Deep Endometriosis Analysis) (11). (Table 1)

1. Utero-ovarian evaluation, describing signs of adenomyosis and presence / absence of endometrioma.
2. Assessment of uterine mobility and description of painful points during exploration.
3. Sign of posterior sliding (assessment of mobility between the posterior wall of the uterus and rectosigmoid) Assess the presence / absence of obliteration of the cul-de-sac
4. Assessment of deep endometriosis in the anterior and posterior compartment

table 1. Extended ultrasound evaluation in cases of coexistence of endometriosis and adenomyosis

The abdominal route mus t be keep in mind, which can be very useful in some cases (very globular uterus, concomitant presence of fibroids, indifferent position, need to rule out renal pelviectasis in cases of deep endometriosis ...)

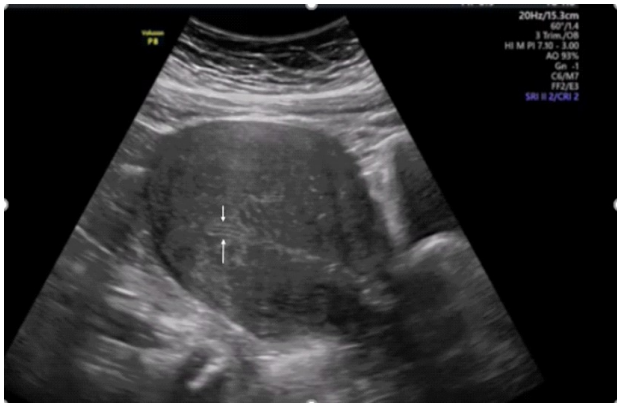

Figure 4.- Adenomyosis. Transabdominal ultrasound showing a globular uterus, with the presence of a large myometrial hypertrophy that affects almost the entire uterine body. The proliferative endometrium is seen between the two arrows. The transabdominal route in these cases of great myometrial hypertrophy may offer better image quality and its use should always be considered.

ECOGRAPHIC CHARACTERISTICS

1.-Globulous uterus. Global subjective increase in uterine myometrial thickness poorly defined and not caused by fibroids. It can be focal or diffuse.

2.-Uterine asymmetries. Thickening of the anterior myometrial wall with respect to the posterior wall or vice versa. There is no validated absolute or relative cut-off point. Comment: The presence of myometrial contractions can temporarily alter uterine morphology. In case of doubt, it is advisable to repeat the examination after 20-30 minutes.

3.-Myometrial heterogenicity and/or linear striations. Myometrial heterogenicity: presence of hyperechoic and hypoechoic areas in the myometrium. Acoustic “fan-shaped” shadows produced by sonic attenuation as it passes through fibrotic areas. Linear striations from the endometrium to the myometrium: hyperechoic lines that cross the thickness of the myometrium, visible from the endometrial-myometrial interface

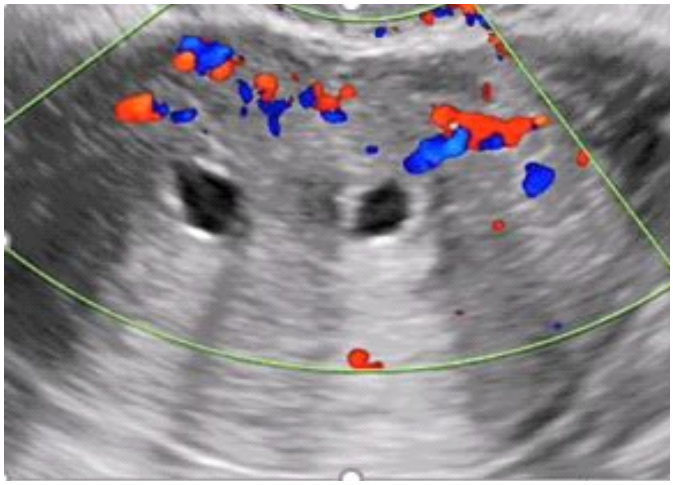

Figure 4 Intra-myometrial cysts. Intra-myometrial non-vascularized anechoic images

4.-Myometrial cysts
Ecolucid rounded images of variable morphology and size located in the thickness of the myometrium, which do not capture color Doppler and therefore do not correspond to vessels. Comment: It is advisable to use Power Doppler or high-definition Doppler

5.- Irregular or interrupted junctional zone
Loss of net contour (fine hypoechoic area) of the myometrial endometrial transition zone (JZ).

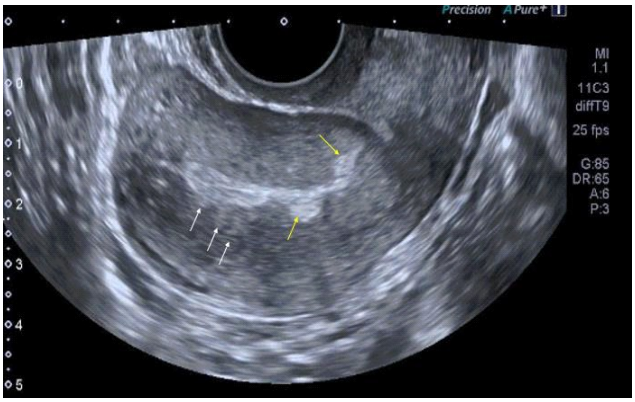

Figure 5. Myometrial islets (yellow arrows) and sub-endometrial lines and buds (white arrows)

CRITERION	ECOGRAPHIC CHARACTERISTICS
Globulous uterus	Global subjective increase in uterine myometrial thickness poorly defined and not caused by fibroids. It can be focal or diffuse.
Uterine asymmetries	Thickening of the anterior myometrial wall with respect to the posterior wall or vice versa. There is no validated absolute or relative cut-off point. Comment: The presence of myometrial contractions can temporarily alter uterine morphology. In case of doubt, it is advisable to repeat the examination after 20-30 minutes.
Myometrial heterogenicity and/or linear striations	Myometrial heterogenicity: presence of hyperechoic and hypoechoic areas in the myometrium. Acoustic "fan-shaped" shadows produced by sonic attenuation as it passes through fibrotic areas. Linear striations from the endometrium to the myometrium: hyperechoic lines that cross the thickness of the myometrium, visible from the endometrial-myometrial interface
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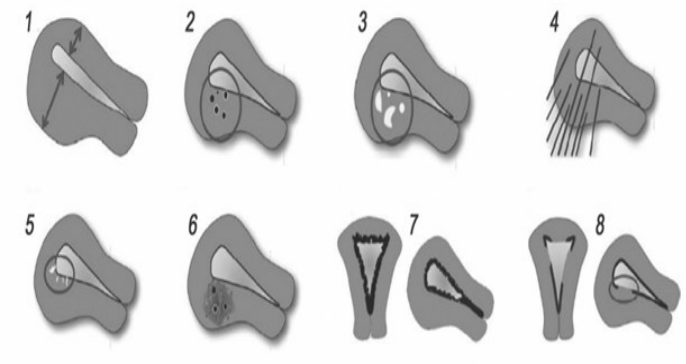

DIAGNOSTIC ACCURACY

If we analyze cases with histological confirmation, ultrasound reaches a sensitivity of 83.8 and a specificity of 63.9%. The incorporation of criteria based on 3D ultrasound, by improving the assessment of the endometrial-myometrial transition zone, can improve the accuracy. For all these reasons, ultrasound is considered the first diagnostic step in the study of adenomyosis, and in certain cases, especially when adenomyosis and fibroids coexist, MRI achieves greater diagnostic precision. Table 3 describes the Sensitivity and specificity of ultrasound based on the ultrasound criteria used.

Ultrasound criteria	Sensitivity (%)	Specificity (%)
Myometrial asymmetry	44	79
Myometrial cysts	54	93
Subendometrial lines and buds	40	92
Disruption ZU	64	73

Table 3. Sensitivity and specificity of ultrasound based on the ultrasound criteria used.

ULTRASOUND REPORT

Van den Bosh et al (14) recommend describing the following aspects:

• **Location** (anterior, posterior, right/left lateral, fundic)

• **Differentiation** (in the sagittal plane)

Focal: lesion surrounded> 25% by normal myometrium.Diffuse: <25%. When in doubt, it will be considered diffuse and if there is one of the two types, it will be defined as mixed.

Adenomyoma: (focal adenomyosis surrounded by hypertrophic myometrium).

• **Type**

Cystic

Non-cystic

• **Affected myometrial layer**

Endometrial-myometrial transition zone or internal myometrium

Middle myometrium (up to the vascular arch)

External myometrium (outside the vascular arcade to serosa)

• **Extension of adenomyosis**.
Mild (<25%)
Moderate (25-50%)
Severe (> 50%).

This classification has yet to be validated with prospective studies. However, although it may be difficult to use in daily, we must bear in mind some minimum criteria (subjective impression of the extension and severity) that help to the clinician in their decision making.

REPRODUCIBILITY

2D ultrasound criteria for adenomyosis have shown good interobserver reproducibility between expert and non-expert examiners (15), while three-dimensional evaluation of JZ do not.

CONCLUSIONS

Adenomyosis is a tissue pathology defined disorder, the clinical diagnosis is mainly based on imaging tests.

Transvaginal ultrasound is considered the initial screening method, leaving MRI for complex cases, or coexistence of large fibroids

There are well-defined ultrasound criteria by the MUSA group that define the diagnosis.

There are many classification systems although there is no general agreement on the use of any of them (16).

The ultrasound report description should be as detailed as possible, especially in cases with clinical impact (infertility, dysmenorrhea, pelvic pain, hypermenorrhea).

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Hysteroscopy and adenomyosis

Virginia Foreste[1], Attilio Di Spiezio Sardo[2]

Department of Neuroscience Reproductive Sciences and Dentistry School of Medicine, Federico II University, Naples, Italy
Department of Public Health, Federico II University, Naples, Italy.

HYSTEROSCOPIC DIAGNOSIS

Adenomyosis is defined as the heterotopic presence of endometrial glands and stroma within the myometrium, with a variable degree of myometrial invasion that can involve the whole uterine wall up to the serosa; it can be associated to a myometrial hyperplasia resulting in the typical increase in uterine size, usually affecting the posterior wall more than the anterior wall of the uterus [1].

There are two forms of adenomyosis, diffuse (associated to a variable whole uterine enlargement) and focal (also known as adenomyoma, defined by a localized mass difficult to distinguish from leiomyoma) [2].

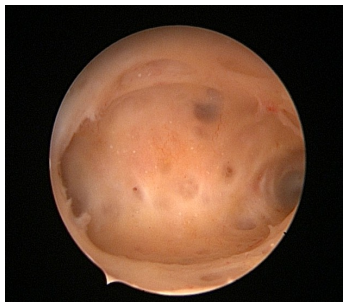

Figure 1. Image captured during hysteroscopy (using a liquid distension medium) suggestive of adenomyosis

Adenomyosis has traditionally been a pathology diagnosed only by the pathologist in hysterectomy specimens [3], but nowadays, the diagnosis of adenomyosis can be done through non-invasive techniques such as transvaginal sonography (TVS)

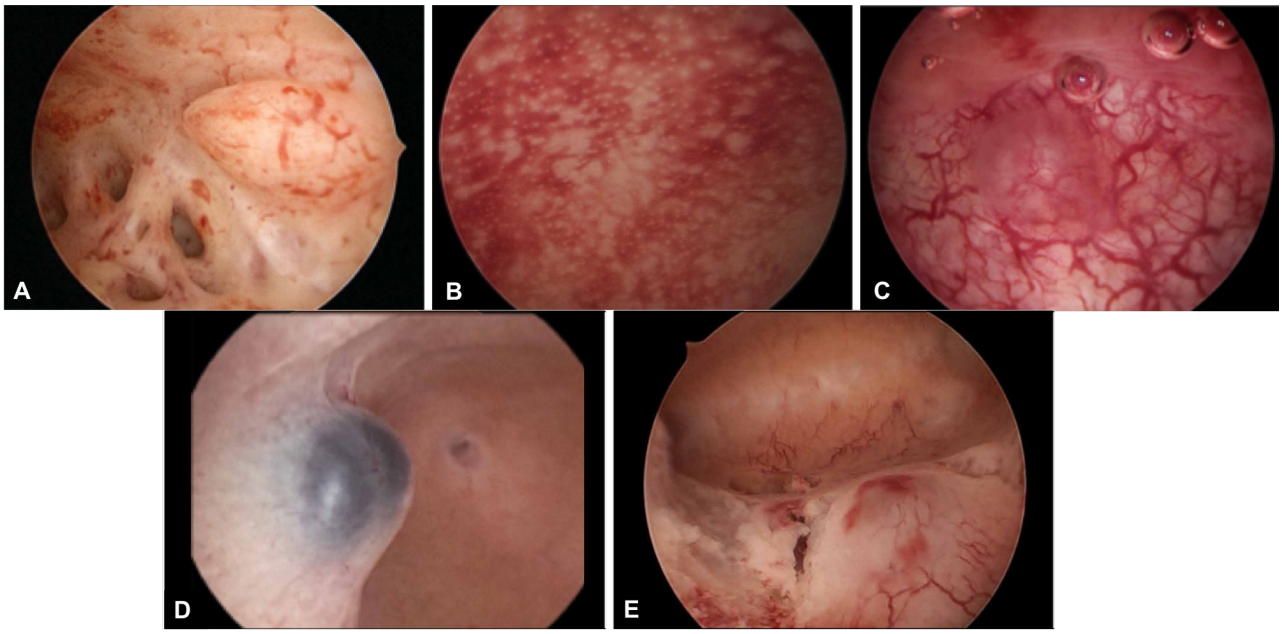

Figure 2. Hysteroscopic signs suggestive of adenomyosis: A. Tiny adenomyotic openings dispersed on an irregular endometrial surface; B. Endometrial mucosa of the uterine fundus markedly hyperemic; note the small glandular cystic dilatations; C. Typical endometrial 'strawberry' pattern: the endometrium shows signs of hyperemia, with bright red areas enclosing white central dots, which are spread over the entire endometrial surface; D. Hemorrhagic cystic lesions exhibiting a dark blue-chocolate brown appearance; E. Adeno-myomatous lesions of the posterior wall assume a fibrous cystic appearance after multiple episodes of intramyometrial bleeding.

[4-8] that can be enriched also by the study of the junctional zone at 3D TVS, [9], magnetic resonance imaging (MRI) [10] and hysteroscopy (figure 1) [11]. At hysteroscopy, adenomyosis should be suspected when one or more of the following signs are found (figure 2) [12]:

- Irregular endometrium with tiny openings seen on the endometrial surface (A);
- Pronounced hypervascularization, due to the presence of an irregular endometrial vascular network (B);
- Endometrial pattern resembling a 'strawberry' (large areas of hyperemic endometrium flushed with white central points) (C);
- Hemorrhagic cystic lesions assuming a dark blue or chocolate brown appearance (D);
- Fibrous cystic appearance of intrauterine lesions (following 3–5 episodes of intramyometrial hemorrhage) (E).

All such superficial vascular anomalies can be adequately evaluated only by decreasing the intracavitary pressure [12]. However, it is important to clarify that hysteroscopy alone, cannot diagnose or exclude adenomyosis because its field of observation is limited to the endometrial surface.

In addition to the direct visualization of the uterine cavity, the hysteroscopic approach offers the possibility of obtaining histological specimens under visual control. Indeed, during hysteroscopy directed biopsies of the endometrium and underlying myometrium can be achieved either using mechanical instruments (biopsy or grasping forceps, scissors) or electrical loop resection; in order to obtain an adequate biopsy to assess the extent of adenomyosis infiltration, a second biopsy deeper into the dent left behind by the first, including only myometrial tissue, can be done [13].

Endo-myometrial biopsy showed a specificity of 78.46% with a low sensitivity of 54.32% the latter mostly related to the high amount of false negative in the cases of deep adenomyosis [14].

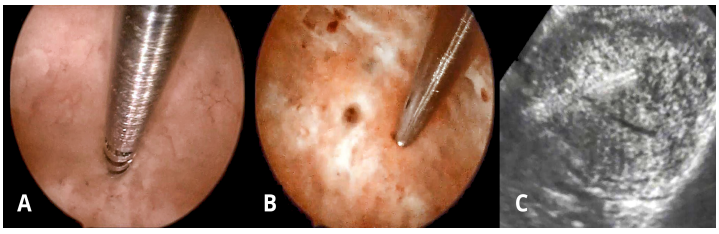

Figure 3. Biopsy sampling of subendometrial myometrium performed hysteroscopically using the Spirotome (Bioncise NV, Belgium) (A–B) under sono-graphic guidance (C).

Currently, the technique of endomyometrial biopsy is also feasible on an outpatient basis using a continuous-flow 15 Fr Bipolar Office Resectoscope (KARL STORZ, Germany) or using an instrument called 'Spirotome' (Bioncise NV, Belgium) (figure 3) that, inserted through the diagnostic outer sheath of TROPHYSCOPE® (KARL STORZ, Germany), under sonographic guidance, allows to obtain biopsy samples of larger size. [15]

Even though, to date, there is still no widely accepted consensus regarding specific diagnostic criteria for resectocopic biopsy sampling in the case of adenomyosis, these patterns, noticeable prior to, during and after resection, can be strongly suggestive of adenomyosis (figure 4) [13]:

- Presence of intramural endometriomas;
- Irregular subendometrial myometrium (spiral and/or fibrotic);
- Contortion of normal myometrial architecture noticeable during resection.

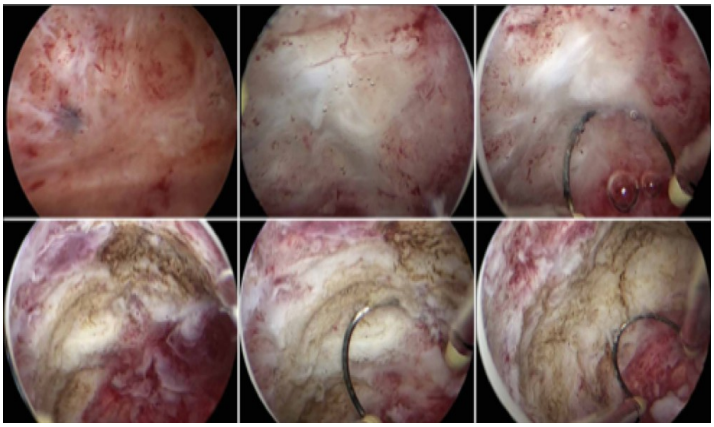

Figure 4. Evacuation of superficial adenomyotic cysts using a 15 Fr bipolar office resectoscope (KARL STORZ, Germany) (A–B). At the end of the procedure (C), the thick, fibrotic wall of the cystic lesion is clearly shown.

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HYSTEROSCOPIC TREATMENT

Hysteroscopy is not a first-line treatment option for women with adenomyosis but may be considered a reasonable choice for patients with childbearing desire [16], because it offers an alternative access for the treatment of cystic adenomyosis while producing minimal tissue damage considering the advantage of leaving the outer myometrium intact [17].

Pre-treatment with GnRH agonists can help reduce the vascularity and bleeding during the surgical procedure and sometimes, it may also help move the adenomyoma into the uterine cavity

[18]. Due to the infiltrative characteristic of the disease with a defective healing of the sub-endometrial zone and an absence of a distinct cleavage plane [19], the hysteroscopic procedure requires particular attention for adequate identification of healthy myometrial tissue; indeed, postoperative control after adenomyomectomy or dissection of an adenomyotic cyst always shows a uterine defect.

According to the setting (outpatient-inpatient technique) or to the extension of adenomyosis (focal or diffuse), different hysteroscopical techniques can be described [20-23].

According the setting:

1- Office Hysteroscopic Treatment

Office hysteroscopy is used in the treatment of adenomyosis only in cases of the superficial focal type. Using mechanical instruments and/or 5 Fr bipolar electrodes (figure 5) or a 15 Fr resectoscope (figure 6) it is possible to evacuate cystic hemorrhagic lesions as well as to enucleate superficial focal adenomyomas of less than 1.5 cm

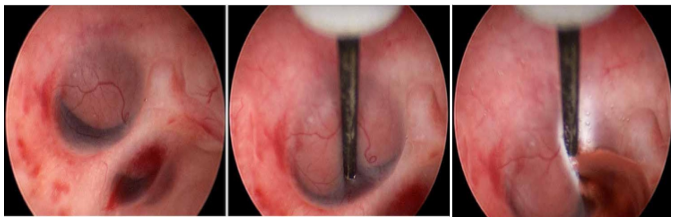

Figure 5. Evacuation of superficial adenomyotic cysts with a 5-Frbipolar electrode (KARL STORZ, Germany). Panoramic image of the uterine cavity (A). The bipolar electrode is positioned at the site of the lesion (B). Upon incision of the cystic wall, a chocolate brown fluid is discharged (C).

in diameter. The technique adopted for adenomyomectomy in an ambulatory setting is the same as that described for enucleation of submucosal myomas with an intramural component, even though, owing to the lack of a distinct cleavage plane, the procedure requires the surgeon to meticulously go through a precautionary exploratory stage for adequate identification of healthy myometrial tissue. Moreover, for cystic lesions localized deeper in the intramural portion (defined as subtype A by Brosens et al. in a recent review on the topic), the Spirotome is a very useful innovation; under ultrasound guidance, access is gained to intramural cystic lesions without visible intracavitary components. The device creates a channel and provides hysteroscopic access to the cystic structure. Treatment by resection or bipolar coagulation can then be performed.

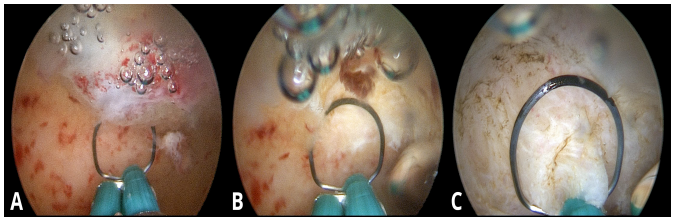

Figure 6. Evacuation of superficial adenomyotic cysts with a 5-Frbipolar electrode (KARL STORZ, Germany). Panoramic image of the uterine cavity (A). The bipolar electrode is positioned at the site of the lesion (B). Upon incision of the cystic wall, a chocolate brown fluid is discharged (C).

2- Resectoscopic Treatment

Resectoscopic treatment is indicated in cases of superficial adenomyotic nodules > 1.5 cm in size (figure 7), and in the presence of diffuse superficial adenomyosis. In the latter case, endometrial ablation may be performed with the additional removal of the underlying myometrium (so-called endomyometrectomy). Deep diffuse adenomyosis, conversely, is not amenable to hysteroscopic treatment. Some authors have demonstrated that, given a deep adenomyosis, resectoscopic treatment not only fails to reduce symptoms of menorrhagia, but may even have adverse effects in that it masks the onset of deep adenomyosis developing below the endomyometrial scar tissue, which may consecutively be prone to malignant transformation.

According the extension of adenomyosis:

1- Focal Adenomyosis

The technique of adenomyomectomy involves that the tissue protruding into the uterine cavity, is incised, evacuated and resected (by slicing) using a resectoscope with a cutting loop. Incases of deeply implanted lesions, the nodule may first be mobilized using various techniques that cause it to migrate into the uterine cavity. These techniques have already been described for the treatment of a submucosal myoma with an intramural component, which is serially resected with a cutting loop until it can be completely removed. The surgical procedure is completed by coagulating the implantation base of the lesion. The goal of surgery is to remove all adenomyotic tissue without causing damage to surrounding

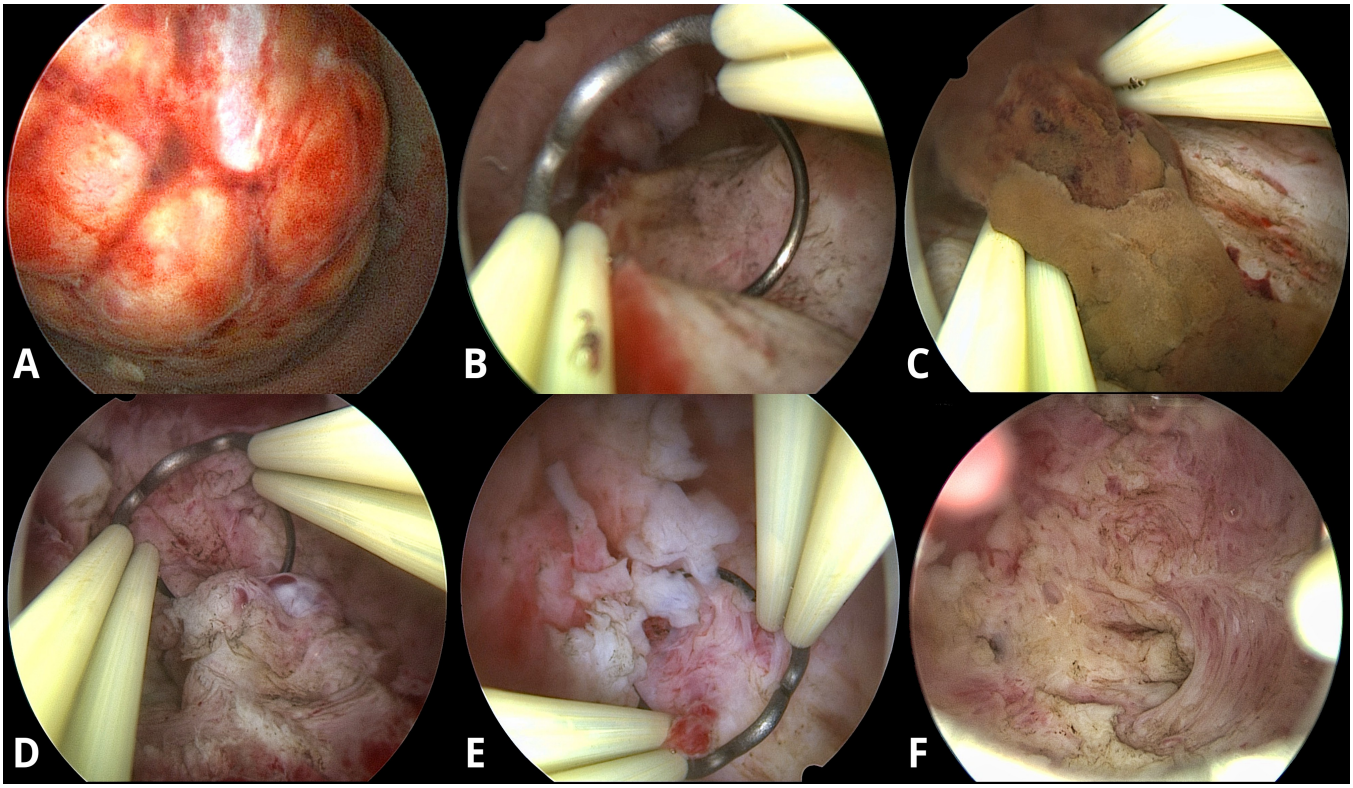

Figure 7. Resectoscopic biopsy with unipolar diathermic loop (KARL STORZ, Germany) of foci suggestive of adenomyosis. A resectoscope with a diathermic loop is effectively used to collect biopsy samples within the endomyometrial thickness for histological diagnostic confirmation and evaluation of the degree of infiltration. Panoramic image of the uterine cavity (A): on the endometrial surface there are overt signs of small cystic hemorrhagic lesions, dark blue in color; also note the irregular subendometrial myometrium. Upon close-up view, in (B), the endometrial mucosa appears markedly irregular with fibrotic areas and exhibits a scarce but irregular vascular distribution. The diathermic loop is guided to the area to be biopsied (C). Resectoscopic biopsy (step I) (D–E): The first incision is passed through the endometrium and the underlying myometrial thickness. During resection, an irregular and fibrotic subendometrial myometrium is noticeable. Resectoscopic biopsy (step II) (F): The second incision advances deeper into the dent created in step I, including only the underlying myometrium. While proceeding with step II, a contorted appearance different from that of the normal myometrial architecture is revealed.

healthy myometrial fibers. However, the lack of a distinct cleavage plane indicating the normal myometrial tissue can make the procedure quite challenging.

2- Diffuse Adenomyosis

Superficial diffuse adenomyosis may be treated with a variable rate of success by means of endomyometrial ablation (endomyometrectomy). The technique differs from the classical method of endometrial ablation in that resection is not limited to the endometrium and the first 2–3 mm of myometrium. Upon resection of the endometrial and superficial myometrial layer, the operator proceeds with continued slicing of the myometrial layer below, until healthy myometrium is visualized, and concludes the procedure by coagulation of endometrial residues. Endomyometrectomy is accomplished using 3-mm or 5-mm straight loops for ablation of the fundus and cornual recesses, as well as classic cutting loops for ablation of uterine walls.

The degree of intramural extension of pathology is correlated with the duration of surgery, its technical difficulty, the risk of incomplete removal of the adenomyotic tissue, the risk of intravasation, and the risks of both uterine perforation and intraoperative hemorrhage.

In case of the persistence and/or recurrence of disease, a second-stage surgical procedure may be performed. However, during preoperative assessment, meticulous care must be paid to the thickness of the myometrium between the outer margin of adenomyosis and the uterine serous surface, which should be thoroughly evaluated by ultrasound.

Worthy of mention is, that endomyometrectomy may give rise to a dissemination and proliferation of ectopic endometrial cells, thereby promoting the progression of pathology, as well as 'de novo' adenomyosis.

As an adjunct to surgery, or as an alternative option, local progestin-based medical therapy by application of a levonorgestrel-releasing IUD may be chosen. The continuous controlled release of LNG, directly at uterine mucosal level, may induce regression of adenomyotic lesions along with a relief of pain symptoms. Unlike deep adenomyotic cells, endometrial cells – located at the adenomyotic surface – are indeed progestin-sensitive. A continuous controlled release of LNG may counteract the potential risk of iatrogenic dissemination of ectopic endometrial cells, secondary to resectoscopic surgery [24].

Operative hysteroscopy may be indicated in cases of superficial adenomyotic nodules and for diffuse superficial adenomyosis. Although it seems that pregnancy rate may improve after conservative surgical treatment of adenomyosis, further research is required to definitively evaluate the benefits of conservative surgery, including hysteroscopic resection of adenomyosis for the treatment of fertility [25-26].

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Cystic adenomyosis

Alejandro González, Victoria María Illia, Milagros Tejerizo

Naval Hospital Buenos Aires. Argentina

Uterine adenomyosis is a benign pathology characterized by the presence of endometrial glands and stroma within the thickness of the myometrium, causing hypertrophy of the smooth muscle fibers around it. On several occasions it occurs in conjunction with endometriosis, a pathology that is considered a different entity, but from which it has not yet been possible to differentiate the etiology.

Classically, two forms of presentation have been described: focal and diffuse. Focal adenomyosis, also called adenomyoma, presents as a circumscribed nodular lesion or as adenomyotic tissue limited to one uterine wall. Diffuse adenomyosis, on the other hand, affects the entire uterus or a large portion of it, with no clear boundary between the pathological tissue and the healthy myometrium.

Although this pathology mainly affects women between 40 and 50 years of age, there is a new entity within it that occurs more frequently in adolescents and young adult women called “cystic adenomyosis”. It usually occurs in patients under 30 years of age with severe dysmenorrhea and persistent pre and post-menstrual pelvic pain that does not respond to common treatment (1).

The pathogenesis is still unknown, there are reports that suggest a congenital cause, since it can present immediately after menarche as asymptomatic uterine cystic lesions.

Cullen was the first to describe adenomyomas with cystic formations inside them in 1908. He defined them as adenomyosis that included cysts with hemorrhagic content without communication with the endometrial cavity, surrounded by myometrial muscle fibers (2).

In 2010 Takeuchi et al. defined the criteria for a new form of adenomyosis called “juvenile cystic adenomyosis” (1):

- Age less than 30 years
- Cystic lesion greater than 1 cm in diameter separated from the endometrial cavity, covered by hypertrophic endometrium visualized with imaging methods
- Association with severe dysmenorrhea.

Histologically it is a cyst lined by endometrium with blood content.

Based on a review of cases, Brosens et al (2015) proposed a new imaging classification system according to the location of the cyst in the uterine wall (Fig. 1) (3):

- Subtype A1: Submucosal or intramural cystic adenoma
- Subtype A2: Cases with polypoid cystic lesion
- Subtype B1: Subserous cystic adenomyosis
- Subtype B2: Cases with exophytic growth
- Subtype C: Accessory masses of uterine aspect

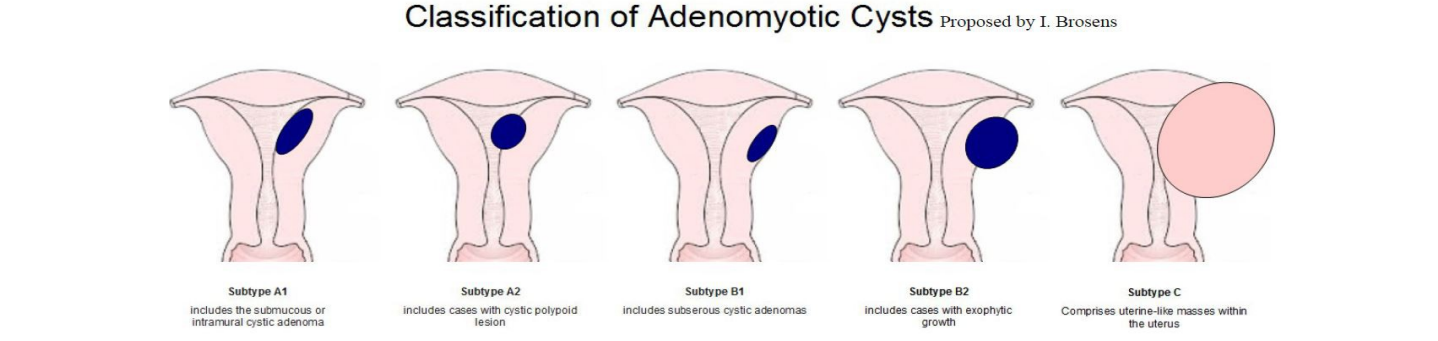
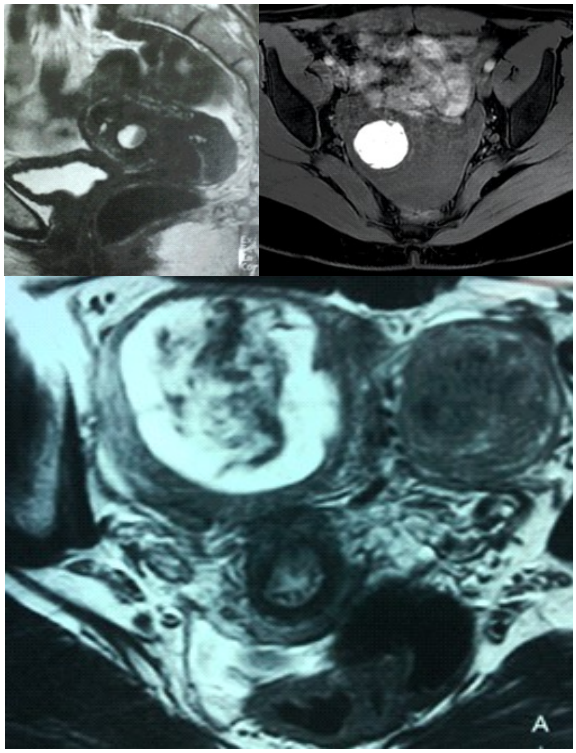


Fig. 1 Brosens, I., Gordts, S., Habiba, M., & Benagiano, G. (2015). Uterine Cystic Adenomyosis: A Disease of Younger Women. Journal of Pediatric and Adolescent Gynecology, 28(6), 420–426

The final diagnosis is always histological. The clinical suspicion is nonspecific since it presents with symptoms common to endometriosis: dysmenorrhea and chronic pelvic pain in young patients, however, it can be diagnosed by transvaginal ultrasound and nuclear magnetic resonance imaging (MRI) (4). By ultrasound, although its appearance is characteristic, similar to an endometrioma, it can be confused with other submucosal, intra-myometrial, or adnexal lesions (5). MRI shows a cystic structure with an internal diameter greater than 1 cm and hemorrhagic content (hyperintense on T1) surrounded by myometrial tissue (hypointense on T2) (6) (Picture 1,2,3). The size can vary during the cycle, due to the presence of estrogen receptors within the lesions.

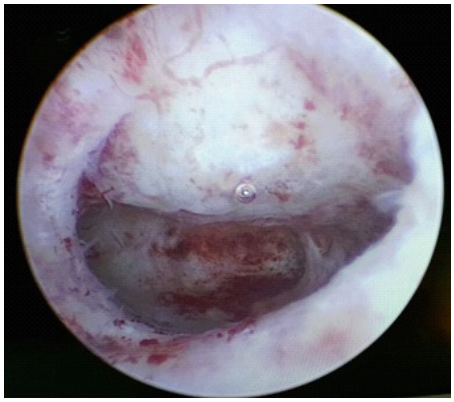


Picture 1: T2 hypointense intramural cystic adenoma. **Picture 2:** T1 hyperintense intramural cystic adenoma. **Picture 3:** Cystic adenoma subtype B2 with exophytic growth in T2

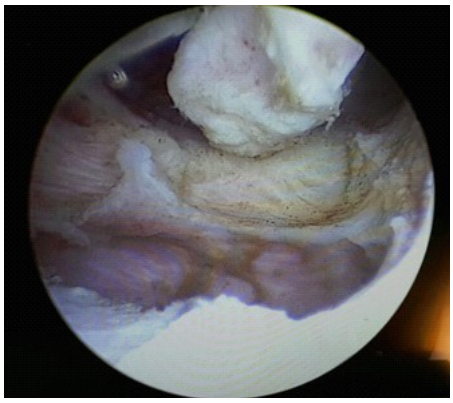
The main differential diagnosis should be made with obstructive uterine malformations. Hysterosalpingography is useful for this, since in patients with juvenile cystic adenomyosis it is possible to observe the patency of both Fallopian tubes, but not in the presence of rudimentary non-communicating uteri (7).

For the therapeutic decision, the desire for future fertility and the severity of the symptoms must be considered. Lack of response to common oral contraceptives and pain medication is common. Regarding treatment with levonorgestrel-releasing intra-uterine device, although it is an effective method to relieve dysmenorrhea in women with adenomyosis (8), there are no reports of its use in women with cystic adenomyosis.

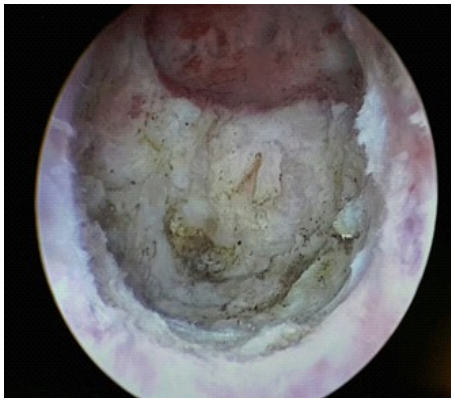
As in all forms of adenomyosis, the curative treatment is hysterectomy. However, when treating mostly young patients, conservative treatment should be attempted and is indicated in patients with persistent symptoms and/or infertility.



Picture 4: Cystic Adenomyoma type A1



Picture 5: Incision and drainage (I&D)

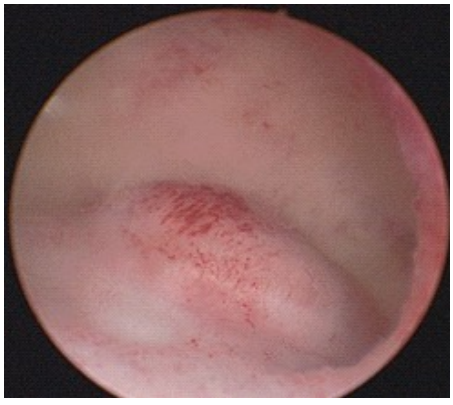


Picture 6: Excision and coagulation of the base

For subtypes A1 and A2, the hysteroscopic approach is indicated, although it has not been properly investigated.

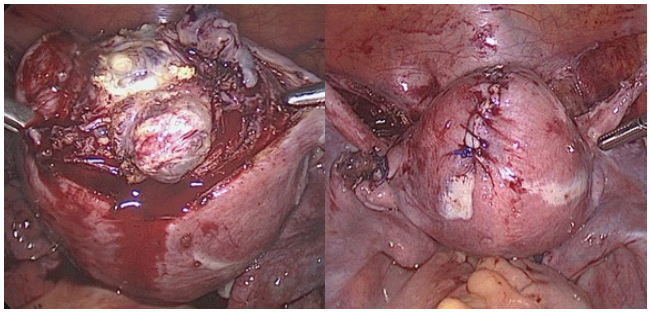
In submucosal-intramural A1 cases, their complete removal should be attempted, but if they are too deep, after opening and evacuation, roller-ball coagulation of the residual endometrium is a valid option (Picture 4,5,6). Certain cases of A1 lesions with intramural adenomyoma may have a laparoscopic indication to achieve its complete removal and not just draining it.

Treatment of type A2 lesions does not differ from a classic polypectomy and its complete removal is recommended (Picture 7).



Picture 7: Adenomyoma Type A2. Polypoid cystic lesion

In cases B1, B2 and C, the most appropriate option for its approach will be laparoscopic. The surgical technique must follow the concepts of approach and reconstruction of a myomectomy, but keeping in mind the difficult identification of the planes (Photos 8 and 9). Surgical treatment has been shown to improve dysmenorrhea and increase the chances of pregnancy (1).



Pictures 8 and 9: Type B2 lesion of exophytic growth and uterine reconstruction in three planes.

CONCLUSION

Cystic adenomyosis is an uncommon presentation of adenomyosis in young patients with dysmenorrhea and pelvic pain refractory to medical treatment. The diagnosis can be made with the combination of transvaginal ultrasound and magnetic resonance imaging. Treatment is surgical: for types A1 and A2 forms, with few exceptions, hysteroscopic treatment is indicated. For the rest, laparoscopic surgery with uterine reconstruction is recommended.

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Non-surgical treatments of adenomyosis

Mykhailo Medvediev

Dnipro state medical university, Ukraine

Adenomyosis especially diffuse forms is very challengeable condition among patients who want to preserve uterus. Unfortunately, surgical organ-sparing methods of treatment are not always feasible and bear the risks of complications including serious complications during pregnancy such as uterine rupture.

It's well-known women with adenomyosis are at higher risk of endometrial cancer (approximately two-fold higher) and higher risk of thyroid cancer (1) . But adenomyosis doesn't considered as a precancerous condition and doesn't require treatment with the sole indication – cancer prevention (1,2) . So, there are two goals for the non-surgical treatment of adenomyosis: symptoms reduction (HMB and pain) and fertility (fecundity) enhancing.

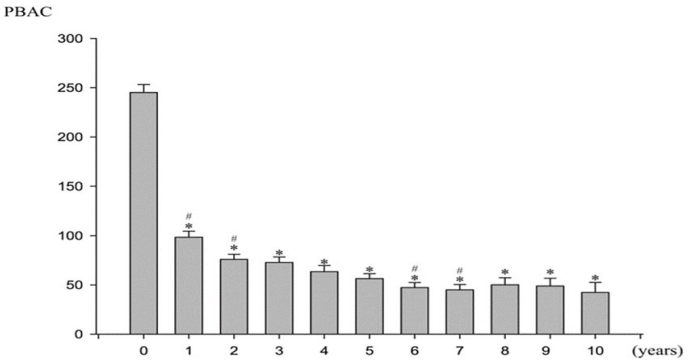
Medical treatment is the first-line treatment option for adenomyosis aiming to relieve symptoms and maintain fertility. It may be effective for reducing heavy menstrual bleeding and dysmenorrhea, as in endometriosis. Currently, several hormonal and non-hormonal options are being used for the symptomatic treatment of adenomyosis.

HORMONAL TREATMENT

There are limited data on medical treatment for adenomyosis, and additional high-quality studies are clearly needed. There are few proposed hormonal medications for the adenomyosis, namely gonadotropin-releasing hormone (GnRH) analogues, progestins, combined oral contraceptives, and non-steroidal anti-inflammatory drugs (3).

For the control of chronic menorrhagia the first line option is (LNG)-releasing intrauterine device (IUD). The LNG-IUD is widely used for its therapeutic effects, including the release of synthetic progesterone at a rate of 20 ug/day.

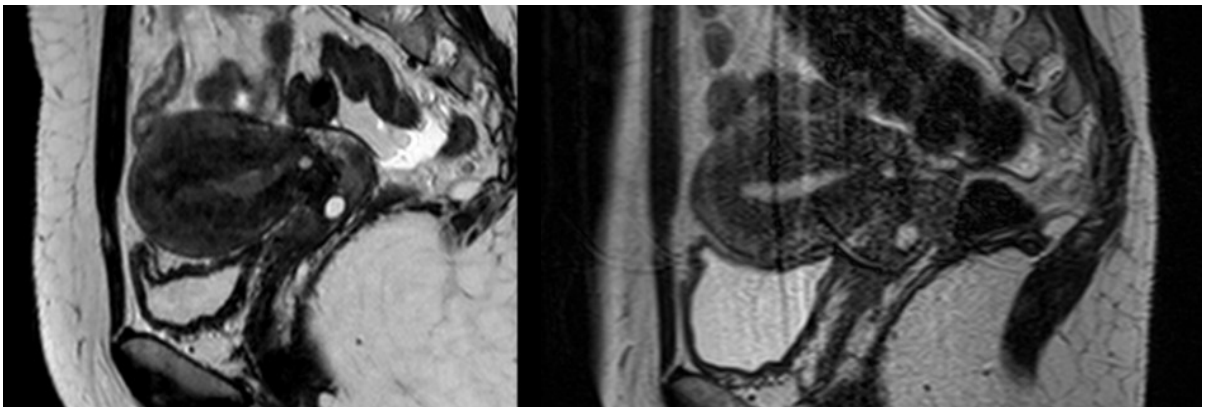
Many published reports have verified its long-term effects in the treatment of uterine adenomyosis The is potent gestagen with direct action on endometrium and myometrium, low systemic levels, and long-acting user-independent administration. It has been shown to improve adenomyosis-associated heavy menstrual bleeding and dysmenorrhea with LNG-IUD (4) .



Picture 1. Changes in subjective assessment score of menstrual blood loss during 10 yr of LNG-IUD treatment (5)

Combined oral contraceptives are widely used off-label for the treatment of heavy menstrual bleeding. However, their effectiveness for the treatment of adenomyosis is not well studied. In one study superiority of LNG-IUD efficacy over COCs in the treatment of adenomyosis has been shown (6) .

Dienogest, widely used for the treatment of endometriosis, has also been shown to be effective in adenomyosis; recent studies have compared the effectiveness of combined oral contraceptives and dienogest for the treatment of adenomyosis. Dienogest and COCs are effective in treating adenomyosis-associated symptoms after 6 months of use but dienogest is more effective. The decrease in uterine volume and uterine artery blood flow may be the cause of the treatment effect (7) .



Picture 2. T2 weighted MRI, sagittal view. Mild diffuse symptomatic adenomyosis before and after 6 months of dienogest (personal archive)

Other hormonal treatment options include gonadotropin-releasing hormone analogs (GnRHa) and the oral GnRH antagonist , which has been used for treatment of adenomyosis alone and for treatment of uterine fibroids with concomitant adenomyosis (8) .

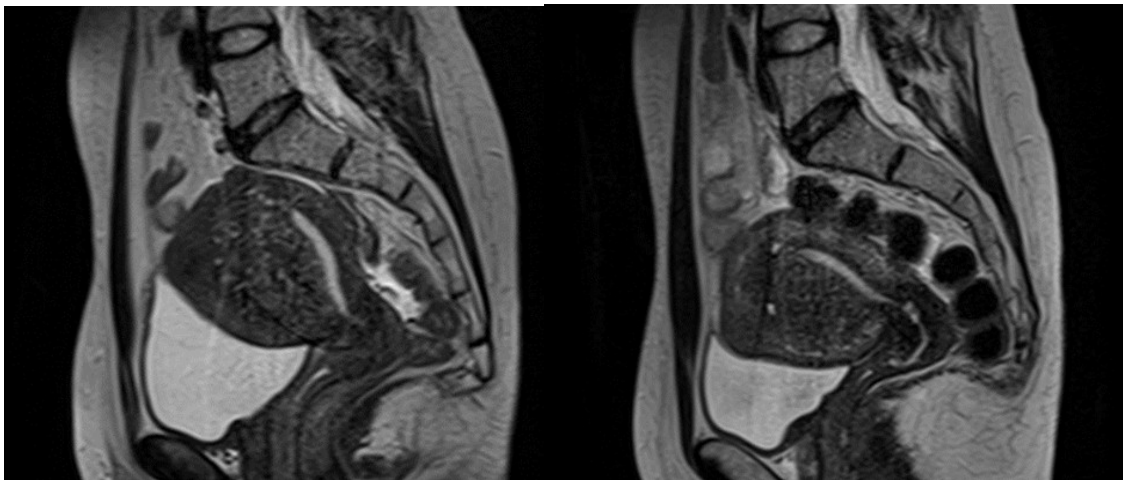
GnRH agonist markedly reduces the angiogenesis and inflammatory reaction associated with adenomyosis and significantly induces apoptosis in tissues derived from women with endometriosis, adenomyosis and uterine myoma. GnRH agonists are effective in the treatment of adenomyosis however, they have a higher incidence of side effects than other hormonal regimens; an additional advantage of GnRH agonists is an improvement of the effectiveness of assisted reproductive technologies. Long-term GnRH agonist treatment in women with adenomyosis before frozen embryo transfer was associated with an increased rate of clinical pregnancy.

When hormonal medications are discontinued, for example when a patient wants to conceive, enlargement of the uterus and recurrence of symptoms are usually documented within six months after discontinuation.

The advantages and disadvantages of various medical methods for the treatment of adenomyosis are presented in the table below.

UTERINE ARTERY EMBOLIZATION

For women who have completed childbirth, uterine artery embolization (UAE) may be effective in reducing symptoms associated with



Picture 3. T2 weighted MRI, sagittal view. Anterior wall adenomyosis before and after 3 months of GnRH agonist (personal archive)

Medication	Advantages	Drawbacks
NSAIDs	Effective against mild pain Non-hormonal composition Safe for women wishing to conceive	Extensive use linked to side effects Inhability to treat underlying causes of pain Qustionable efectivenessagainst HMB
COCs	Relatively effective in relieving pain Fewer side effects than other drugs	Limited efficacy in reducing HMB and uterine volume Risk of Thromboembolic events
Progestins	Alleviate local Hyperestrogenism Relieve pain symptoms Possibility of long-term symtom management Ample evidence in favor of LNG-IUD use	Inefffective in about one-third of patients Frecuently cause menorrhagia at variaying severity Doubful efficacy in diminishing uterine volume
UPA	Lower serum stradiol levels May reduce HMB	Reports of symptoms and imaging feature exacerbation Limited to restricted medications by the EMA
GnRH Agonists	Alleviate pain Induce amenorrhea Reduce uterine volume and JZThickness Benefitial as pre-treatment in infertile patients	Flare-up effect Severe hypoestrogenic side effects Long-term administration not indicated even with add-back therapy
GnRH Antagonists	Easy an tolerable oral administration Rapid action skkiping initial flare-up Effectively reduceHMB and pain symptoms	Loss of BMD at higgh doses Less efficient when combinedwith add-back medication

adenomyosis. The UAE is also suitable for women who refuse or have contraindications to hysterectomy or have not received hormonal treatment.

The efficacy of UAE for treatment of adenomyosis has been established in the short-term but mid- to long-term durability is less clear. While some studies demonstrated high rates of symptom recurrence, with only 45–57% women remaining symptom free at 2–3 years, others reported maintenance of clinical success in 70–76% at 3–5 years. Recent long-term study has confirmed that UAE is a durable, definitive treatment for adenomyosis in 80% of women. Hysterectomies were avoided in 93% of women. UAE did not bring forward menopause.

OTHER TREATMENTS

Some other minimally invasive uterine-sparing therapies, including those used to treat uterine leiomyoma, have shown some efficacy in the treatment of adenomyosis. Case series of MRI-guided focused ultrasound (HIFU) surgery show both symptom improvement and uterine volume reduction with 6 to 12 months of follow-up.

COMBINATION OF TREATMENTS

The combination of GnRH-a and HIFU treatment significantly decreased serum CA125 levels, volumes of uterine, adenomyotic lesion and menstrual blood, as well as dysmenorrhea scores, and improved the clinical outcomes compared with the HIFU ablation alone in patients with adenomyosis .

CONCLUSION

Despite the large number of non-surgical methods of adenomyosis treatment, today the data on their effectiveness are quite limited. New drugs are being developed. Existing medications such as dopamine agonists, oxytocin antagonists as well as various combinations of the treatment of adenomyosis are studied. Perhaps in the future we will get opportunities for more effective treatment of adenomyosis using various more effective medications as well as new optimized strategies for selecting patients and combinations of existing approaches to therapy.

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Endometrial Ablation In Adenomyosis

Thiago Guazzelli

Hospital de VN Cachoeirinha, São Paulo, Brazil

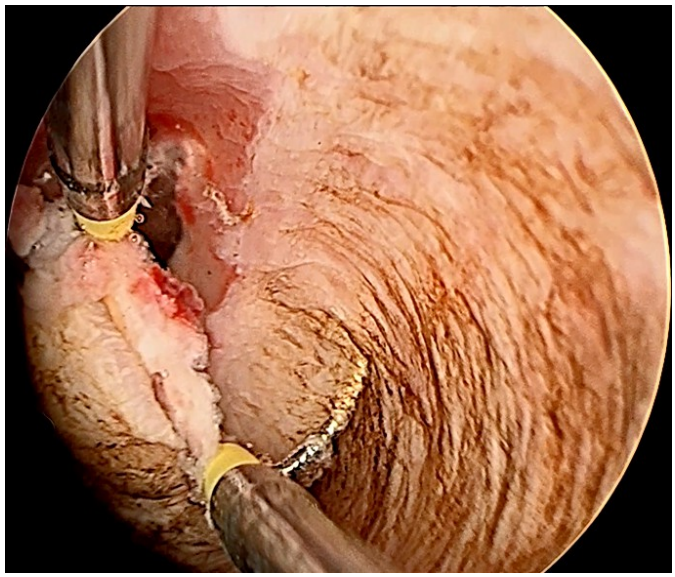
There are a variety of therapeutic options for patients with abnormal uterine bleeding (AUB) and heavy menstrual bleeding (HMB). Endometrial ablation (EA), which is the surgical destruction of the uterine lining, has become an increasingly popular treatment since it is minimally invasive and avoids chronic use of medications when the procedure is successfully done. (1, 2)

A revised terminology system for AUB in nongravid reproductive-age patients was introduced in 2011 by the International Federation of Gynecology and Obstetrics (FIGO). The classification system is referred to by the acronym PALM-COEIN (polyp, ADENOMYOSIS, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified). (3)

Adenomyosis is one of the most common etiologies of HMB. Although these conditions may be treated with surgery, medical management represents appropriate initial treatment and indeed, many patients prefer initial medical management. For patients with HMB associated with adenomyosis, EA may be less effective than in other conditions. (4)

Adenomyosis is not a contraindication to EA, although patients with this condition may have a lower treatment success rate. A retrospective study of 816 patients who were followed for five years after EA reported that patients with a preoperative ultrasound suggestive of adenomyosis had a 1.7-fold increased risk of subsequent hysterectomy or repeat EA. (5)

McCausland et al demonstrated that superficial adenomyosis can be treated definitively with ablation but deep adenomyosis responds poorly to this technique. Patients without or with only minimal endometrial penetration of <2.5 mm (superficial adenomyosis) have good results from the ablation. Patients with deep endometrial penetration of >2.5 mm (deep adenomyosis) usually have persistent problems and should be offered hysterectomy over repeat ablation. Magnetic resonance imaging or ultrasound may be an appropriate preoperative screening tool to determine the depth of adenomyosis and hysterectomy should be considered when demonstrates deep adenomyosis. (6, 7) Some authors have demonstrated that, given a deep adenomyosis, resectoscopic treatment not only fails to reduce symptoms but may even have adverse effects in that it masks the onset of deep adenomyosis developing below the endomyometrial scar tissue, which may consecutively be prone to malignant transformation. (8)



EA and Levonorgestrel Intrauterine Dispositive

EA with concomitant insertion of a 52 mg levonorgestrel intrauterine dispositive (LNG IUD) appears to be safe and to result in a high rate of amenorrhea, based upon several small observational studies. The largest study was a retrospective cohort study of 53 patients who

underwent insertion of an LNG IUD on completion of EA and confirmation of adenomyosis; a control group of 42 patients underwent endometrial resection only. At one-year follow-up, patients in the LNG IUD group had higher rates of amenorrhea (100 versus 9 percent) and resolution of dysmenorrhea (90 versus 20 percent). There were no complications in the LNG IUD group that resulted in removal of the device. None of the patients in the LNG IUD group had a subsequent procedure to control uterine bleeding compared with eight patients in the control group. (9,10)

A prospective study of 43 patients with adenomyosis that compared EA combined with the LNG IUD versus LNG IUD alone found a significant reduction in menstrual flow in the combined group at 3, 6, and 12 months posttreatment. EA with LNG IUD was associated with a significant reduction of number of days bleeding, as well as an improved amenorrhea rate (40%) compared with EA alone (26%). (11)

CONCLUSION

Preoperative magnetic resonance or ultrasound may be considered to determine the depth of adenomyosis. EA is an efficient minimally invasive treatment for superficial adenomyosis, but not for deep adenomyosis.

Conservative uterine-sparing treatments of adenomyosis appear to be feasible and efficacious. An improvement of dysmenorrhea and menorrhagia is achieved in more than 81% and 50% of the patients, respectively. (12)

EA and LNG IUD may be considered. This association increase the rate of success when comparing to only medical or hysteroscopic treatment.

Hysterectomy remains the gold standard treatment for symptomatic adenomyosis if fertility is not an issue. (8)

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Adenomyosis and its impact in fertility

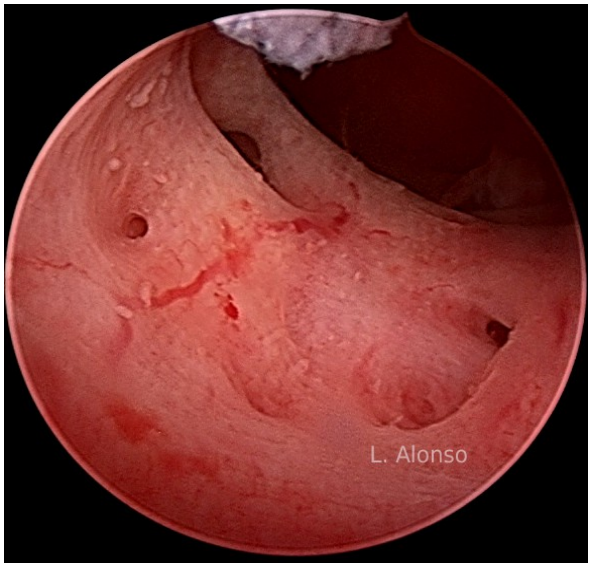
Elena Puente

Assisted Reproduction Unit, Fertia Clinic. Málaga, Spain

INTRODUCTION

The first detailed pathologic description of endometriosis and adenomyosis, was published in Vienna in 1860 by Karl Freiherr von Rokitansky. Adenomyosis is a benign uterine disease defined as the presence of heterotopic endometrial glands and stroma in the myometrium with adjacent smooth muscle hyperplasia.

It is a common benign uterine disorder, it has been considered a histopathological diagnosis made after hysterectomy, classically performed in perimenopausal women with abnormal uterine bleeding (AUB) or pelvic pain with a prevalence of 30%. Until recently, adenomyosis was a clinically neglected condition. Nowadays, adenomyosis may also be diagnosed by non-invasive techniques, because of imaging advancements, such as magnetic resonance and transvaginal ultrasound. Thus, a new epidemiological scenario has developed, and adenomyosis has become a multifaceted disease diagnosed by imaging techniques in young women with abnormal uterine bleeding, infertility or pelvic pain, even in asymptomatic women. It is often diagnosed in association with other gynecological comorbidities such as endometriosis and uterine fibroids.



ADENOMYOSIS AND FERTILITY

Several studies have shown a link between adenomyosis and infertility, but the precise mechanisms involved are not clearly stablished. Eutopic and ectopic endometrial tissues of patients with adenomyosis present different expression of genes associated with apoptosis and angiogenesis such as Bcl-2 and VEGF (1), there is higher expression of VEGF involved in angiogenic processes as well as vascular permeability, a higher expression of Bcl-2, anti-apoptotic molecule, which is present throughout the secretory phase , this overexpression increases cells resistance to apoptosis , which could affect the remodeling of endometrial tissue during implantation of the blastocyst and the development of the placenta (2).

Other factors involved in implantation appear altered such as, increased levels of prostaglandins in the ectopic endometrial epithelium, higher expression of aromatase cytochrome P450 in the eutopic endometrium , decreased integrin beta 3, osteopontin, and leukemia inhibiting factor, and impaired HOXA-10 gene function during the implantation window. It has also been described a decreased expression of progesterone receptors A and B in ectopic endometrium, possibly related to epigenetic changes. This progesterone resistance could lead to an abnormal expression of progesterone receptor-related genes, and reduced expression of implantation-related genes (3).

Besides these changes on endometrial genes related with implantation, women with adenomyosis present impaired uterotubal transport, higher level of nitric oxide in the uterine cavity , altered contractility , and altered uterine cavity volume among other factors with an important negative impact in fertility.

Six different recent meta-analyses have evaluated impact of adenomyosis on pregnancy complications as well as fertility outcome after assisted reproduction and natural conception.

First one by **Maheshwari** in 2012 (4), stablished the need for accurate diagnosis, as given the delay of pregnancy and better diagnostic facilities the likehood of diagnosis of adenomyosis in the infertile population increases.

Vercellini in 2014 (5) found that women with adenomyosis had a 28% reduction in the like hood of clinical pregnancy and increased risk of early pregnancy loss, so screening for adenomyosis before attempting medical assisted reproductive procedures should be encouraged.

Margit Dueholm in 2017 (6) also found reduced implantation, early pregnancy loss and preterm birth related to adenomyosis, in their meta-analysis some studies indicate and adverse implantation outcome in relation to the extent of JZ change (7). Studies evaluating morphology of the endometrial cavity showed moderate distortion in 23% of women and 10% had a severe impact with a pseudo T-shaped uterus (8).

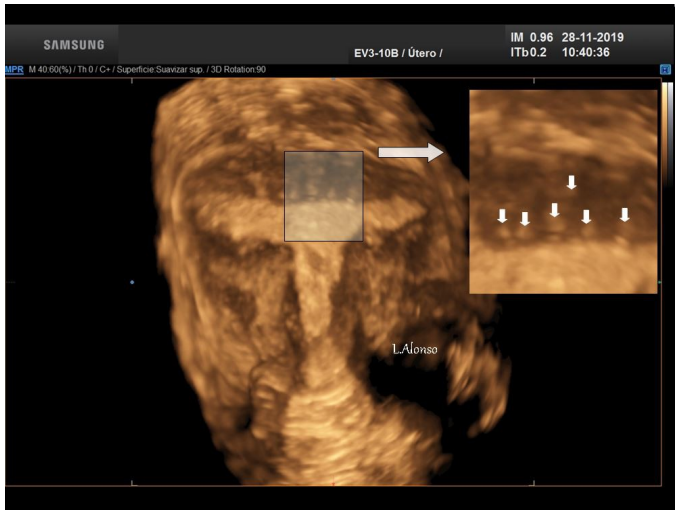
Younes et al (9) in 2017 published a meta-analysis on 11 different studies where it appears that diffuse adenomyosis fares worse than focal or localized adenomyosis. They also found that women with adenomyosis had a higher miscarriage rate that those without adenomyosis, presence of adenomyosis was associated with a 41% decrease in life birth rate. And conclude that adenomyosis has a detrimental effect on IVF clinical outcomes.

Later on the group by **Horton** (10) in 2019 published another meta-analysis that showed reduced clinical pregnancy rate, reduced life birth rate and increase miscarriage rate in women with adenomyosis compared to controls. A lower implantation rate after IVF, though no difference in oocyte yield. A higher risk for late pregnancy and neonatal complications such as preterm delivery, placenta praevia, pregnancy induced hypertension, postpartum hemorrhage.

The most recent meta-analysis published in 2021 by Konstantinos **Nirgianakis** (1), finds that adenomyosis is significantly associated with a lower pregnancy rate after treatment with assisted reproductive technology, higher miscarriage rate. And it is also significantly associated with an increased risk of pre-eclampsia, preterm delivery, caesarion section, fetal malpresentation, small for gestational age and postpartum hemorrhage.

TREATMENT

At present , Gn-Rh-a pretreatment before natural conception is suggested in women without diminished ovarian reserve. Gn-Rh agonists transiently suppress the hypothalamus-pituitary gland ovary axis, and induce hypoestrogenic effect, with resultant shrinkage of adenomyosis. It has also been shown that Gn-Rh agonists , can exert antiproliferative and apoptotic effects on cultured endometriotic cells and certain cancer cells derived from reproductive organs (12), treatment with Gn-Rh agonist significantly suppressed proliferation of cells derived from endometrium and pathologic lesions in patients with adenomyosis.



There are no randomized controlled trials comparing different IVF protocols for women with adenomyosis. Although many authors publish higher pregnancy rate and life birth rate adopting an ultralong Gn-Rh -a protocol. Use of Gn-Rh agonist induces apoptosis and reduces the inflammatory reaction and angiogenesis. The disadvantages of using long term GnRH- are longer ovarian stimulation, higher gonadotropin doses, lower oocyte yield. So its use is reasonable in patients with normal ovarian reserve, especially in patients with diffuse adenomyosis. Other authors consider that it is more cost effective the use of GnRh analogue before frozen embryo transfer especially in women with low ovarian reserve. In the study by Niu (13) frozen embryo transfers in women with adenomyosis, after use of long term GnRh agonist plus hormone replacement therapy, had significantly higher clinical pregnancy rate , implantation rate and ongoing pregnancy than the HRT group with no pretreatment with GnRH-a.

Other therapeutical options as pretreatment before frozen embryo transfer in women with adenomyosis have been proposed , the use of levonorgestrel releasing intrauterine system three months before, conventional FET cycle has also shown higher implantation rate, clinical pregnancy rate, and lower miscarriage rate in comparison to patients with adenomyosis and conventional FET cycle (14).

CONCLUSIONS

It can be concluded that adenomyosis is associated with negative effects on fertility after ART, and independently of the mode of conception adenomyosis is also associated with adverse pregnancy and neonatal outcomes. There is an urgent need of proper counselling prior to ART and close monitoring of pregnancy in patients with adenomyosis. Gynecologist should be aware of these risks, in order to stablish proper pregnancy controls in these patients enabling an early diagnosis and therapy for pregnancy complications. Personalized ART therapies should be applied to these patients in order to improve their chances to conceive

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