

Actual considerations concerning the contribution of hysteroscopy to diagnosis and treatment of adenomyosis in infertile patients

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Abstract

Introduction and objective. A classical histological definition for adenomyosis is the invasion of the gland or endometrial stroma miometer, more than 2,5 mm from the junctional area, accompanied by the adjacent muscular tissue hyperplasia. Adenomyosis is a gynecological pathology commonly found in women of reproductive age and is a frequent cause of infertility. Hysteroscopy is not the primary diagnostic and therapeutic method for adenomyosis, but may be useful in some cases. **Methodology.** This paper is a systematic review of the literature which aims to highlight the role of hysteroscopy in the diagnosis and treatment of adenomyosis in infertile patients. **Results.** Hysteroscopy is a useful therapeutic and diagnostic method for infertile patients with adenomyosis, as many specialized studies show. **Conclusions and discussion.** Hysteroscopy is a useful method of diagnosis and treatment only in well-selected cases of focal and diffuse superficial adenomyosis. Exploring the uterus should not be limited to hysteroscopy in infertile patients with adenomyosis.

Keywords: adenomyosis, hysteroscopy, infertility, IVF, ICSI

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Rezumat

Introducere și obiectiv. O definiție histologică clasică pentru adenomioză este invazia miometrului de glande sau stromă endometrială mai mult de 2,5 mm de la nivelul zonei joncționale, acompaniată de hiperplazia țesutului muscular adiacent. Adenomioza este o patologie ginecologică frecvent întâlnită la femeile de vârstă reproductivă și este o cauză frecventă de infertilitate. Histeroscopia nu este principala metodă diagnostică și terapeutică în cazul adenomiozei, dar poate fi utilă în anumite cazuri. **Metodologie.** Lucrarea de față este un review sistematic al literaturii de specialitate, cu scopul de a evidenția rolul histeroscopiei în diagnosticul și tratamentul adenomiozei la pacientele infertile. **Rezultate.** Histeroscopia este o metodă utilă atât terapeutică, cât și diagnostică la pacientele infertile cu adenomioză, așa cum arată numeroase studii de specialitate. **Concluzii și discuție.** Histeroscopia este o metodă utilă de diagnostic și tratament doar în cazuri bine selecționate de adenomioză focală și difuză superficială. Explorarea uterului nu ar trebui să se limiteze doar la histeroscopie în cazul pacientelor infertile cu adenomioză. **Cuvinte-cheie:** adenomioză, histeroscopie, infertilitate, FIV

Considerații de actualitate privind rolul histeroscopiei în diagnosticul și tratamentul adenomiozei la pacientele infertile

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Introduction

In 1860, Karl Freiherr von Rokitansky described adenomyosis as a "fibrous tumor containing gland similar to endometrial glands"⁽¹⁾. The current definition of adenomyosis is "benign pathology of the uterus characterized by the invasion of the myometrium by endometrial and stromal glands"⁽²⁾. The most common symptoms that patients present with are: dysmenorrhea, menometroragies, infertility, and dyspareunia. One third of women diagnosed with adenomyosis are however asymptomatic⁽³⁾.

Adenomyosis is commonly diagnosed over the age of 40 years⁽⁴⁾. More and more women postpone the moment of conception until 35 years old⁽⁵⁾. This is relevant in the context of the adenomyosis in patients who desire a pregnancy⁽⁶⁾. Improving diagnostic imaging methods allows the detection of adenomyosis in a significant proportion of

previously diagnosed patients with unknown infertility⁽⁷⁾. Since radical surgery is not an option for pregnant women with adenomyosis, many minimally invasive medical and surgical treatments are proposed and compete to prove their primacy in the treatment of adenomyosis in infertile patients^(8,9). Hysteroscopy is a diagnostic and therapeutic option for infertile patients, strongly under debate in recent years in terms of efficacy in patients with adenomyosis who wish to achieve a pregnancy and with repeated implantation failures⁽¹⁰⁾.

What is adenomyosis?

A definition of adenomyosis still valid today dates back to 1972, when Bird et al. described this pathology as a "benign invasion of the myometrium by the endometrium, which produces diffuse enlargement of the uterus and is

explained microscopically by the presence of endometrial glands and stroma surrounded by adjacent myometrial hypertrophy". The thickness of the invasion is another important aspect of the definition⁽¹¹⁾.

When the physiologic barrier of endometrial basal layer and myometrium is exceeded, the myometrium is invaded by endometrial glands that give birth to ectopic intra-myometrial glands. The result of this invasion is hypertrophy and adjacent myometrial hyperplasia⁽¹²⁾.

Usually, the diagnosis of adenomyosis is based on the histological outcome. This is particularly possible following examination of the parts resulting from total hysterectomy. It was initially believed that adenomyosis is diagnosed exclusively in multiparous patients⁽¹³⁾. In about 80% of cases, adenomyosis is present simultaneously with endometriosis and uterine fibroids^(14,15). The incidence of adenomyosis varies between 5% and 38.5% in the literature. This variation depends on the diagnosis method^(11,16). The prevalence of adenomyosis varies in the literature between 10% and 90%⁽¹⁷⁻²⁰⁾.

The prevalence of adenomyosis is dependent on age, parity, and association with endometriosis⁽²⁰⁾. The accurate prevalence of adenomyosis in patients with infertility is more difficult to assess because most prevalence studies come from elderly women after hysterectomy. Moreover, most existing studies show the prevalence of adenomyosis in symptomatic patients⁽¹⁹⁾. For example, the prevalence of adenomyosis in patients with dysmenorrhea is approximately 53%^(13,21). The prevalence of adenomyosis is estimated to be about 30-40% in infertile women using assisted human reproductive techniques. The negative effect of adenomyosis in terms of *in vitro* fertilization (IVF) results is well known^(22,23).

Risk factors for adenomyosis

As mentioned before, adenomyosis frequently coexists with other gynecological disorders and is more common in women in the fifth decade of age⁽⁵⁾.

A study on 160 women showed a higher frequency in multiparous patients, in patients with at least one spontaneous abortion or having a cervical curettage, in smokers and in irregularly-menstrual cycle patients.

The explanation for the association of adenomyosis with multiparity could be the trophoblastic invasion of the myometrium during pregnancy. There are many controversies about caesarean section and adenomyosis^(4,24,25).

Other studies support the impact of sex hormones on the etiology of adenomyosis: the presence of estrogen receptors, along with various progesterone receptors and androgens receptors in adenomyotic tissue. It seems that the number of progesterone receptors would be higher than of estrogenic ones^(26,27). In terms of smoking, some authors claim that it is a risk factor for adenomyosis (especially smoking for over 10 years)⁽²⁴⁾, while other authors claim that smoking is a protective factor for adenomyosis by lowering estrogen levels in the blood of smoking patients⁽⁴⁾. Vercellini includes endometriosis and surgical procedures (both uterine curettage and caesarean section) among the risk factors associated with the presence of adenomyosis⁽¹²⁾.

Adenomyosis classification

There are many proposed classifications of adenomyosis, but there isn't a complete one that takes into consideration all of the below aspects.

Histologically, based on the extent of the lesions, Charles et al. divides the adenomyosis into three grades as following:

- Grade I – sub-basal endometrial stratum.
- Grade II – up to mid-myometrium.
- Grade III – beyond mid-myometrium⁽²⁸⁾.

G. Kunz et al., in 2007, classified adenomyosis based on the thickness of junctional zone (JZ) on MRI (Magnetic Resonance Imaging):

- Hyperplasia of JZ – 8-12 mm (partial or diffuse).
- Adenomyosis – >12 mm (could involve the outer myometrium; several high-signal intensity foci in the myometrium).
- Adenomyomas – several masses within the myometrium with no visible margins of primarily low-signal (could involve the fallopian tube, the bladder; retro-cervical or retro-vaginal)⁽²⁹⁾.

Based on the disease localization, Y. Kishi et al. finds four subtypes of adenomyosis and classifies them based on MRI specification: intrinsic, extrinsic, intramural and indeterminate⁽³⁰⁾.

Based on both histological and clinical criteria, for choosing the optimal surgical treatment, Gordts et al. classifies the adenomyotic lesions as follows:

- Diffuse – JZ thickening and extension of endometrial glands in the outer myometrium.
- Focal – adenomyotic masses/cysts within the myometrium.
- Polypoid adenomyomas (both typical and atypical).
- Adenomyosis of the cervix.
- Retroperitoneal adenomyosis⁽³¹⁾.

The junctional zone (JZ) definition

Even though the uterine myometrium is considered an assemblage of homogenous smooth muscle fibers, there are MRI findings describing two different zones within. The first one is the junctional zone which can be considered the sub-endometrial myometrium and the second one the outer myometrium. There are significant functional and structural differences between the two of them. A diffuse thickening of the junctional zone is believed to be a distinctive feature of adenomyosis and consists of a disarrangement of smooth muscle fibers⁽³²⁾.

This JZ is thought to be the imaging component, the "myosis", while the histological component is the invasiveness of the endometrial glands in the myometrium, the "adeno".

Therefore, the JZ myometrium is much more related to the endometrium than the outer part of the myometrium. Like the former one, it is from müllerian origins and depends on the hormone variations dependent on the menstrual cycle. Also, both the endometrium and the JZ myometrium reach a maximum growth between days 8 and 16 of menstrual cycle and play a key role in implantation and placentation by trophoblast invasion⁽³³⁾.

Adenomyosis and infertility

Numerous studies have shown that adenomyosis is associated with decreased results following assisted reproduction techniques (ART), FIV/ICSI (*in vitro* fertilization/ intracytoplasmic sperm injection) in terms of decreasing implantation rate, increased risk of spontaneous abortion, decreasing live birth rates^(6,22,33,34). A study of 345 patients who performed PGS (Preimplantation Genetic Screening) showed the association of adenomyosis with an increased rate of early spontaneous abortion independent of maternal age and genetic quality of the embryo⁽³⁵⁾. A meta-analysis that included six studies and nearly 10,000 patients showed increased risk of premature birth, premature rupture of membranes, low birth weight, spontaneous abortion and preeclampsia in adenomyosis women compared to women without this pathology. The same study demonstrates that there is no correlation between adenomyosis and an abnormal fetal presentation⁽³⁶⁾.

How does adenomyosis influence fertility?

The fact that adenomyosis affects pregnancy rate is described by numerous studies, but the mechanisms by which fertility is affected are strongly still under debate⁽³⁷⁻⁴⁰⁾.

One of the mechanisms by which adenomyosis could affect embryo implantation in patients with adenomyosis is explained by K.P. Tremellen and P. Russell. A higher density of macrophages and killer cells in the endometrial stroma was observed in patients with diffuse adenomyosis or localized adenomyoma⁽⁴¹⁾. Brosens et al. explains the negative influence of adenomyosis in IVF cycles by increasing local estrogen production due to overexpression of P450 aromatase⁽⁴²⁾. Modification of utero-tubal peristalsis and impaired sperm transport were explained as a mechanism of infertility in adenomyosis by S. Kissler et al. in 2006. This mechanism is particularly valid in the presence of diffuse adenomyosis in the patients with normal tube-ovarian anatomy⁽⁴³⁾.

The inflammatory reaction produced by prostaglandins and cytokines also causes damage to uterine peristalsis and damages sperm transport⁽⁴⁴⁾. The formation of free radicals affecting the oocytes and the embryos is explained by another study. Ota et al. states the expression of antigens at the surface of endometrial cells in patients with adenomyosis, which results in an increase number of macrophages and immune cells that result in immunoglobulin and complement deposition. Also, immune cells activate secreted cytokines that affect the quality of oocytes and embryos in patients with adenomyosis⁽⁴⁵⁾.

The decrease in endometrial sensitivity is explained by several mechanisms, as follows. The first mechanism is the presence of increased amounts of free radicals that attempt to explain how adenomyosis affects fertility⁽⁴⁶⁾. Leukemia inhibitor factor and interleukin 11 levels have been shown to be higher in infertile patients with adenomyosis. This is also incriminated in decreasing endometrial receptivity⁽⁴⁷⁾. Another mechanism that explains repeated implantation failure in women with adenomyosis is the lower LIF (Leukemia Inhibitory Factor) expression in the secretory phase in women with adenomyosis⁽⁴⁸⁾.

How does adenomyosis influence the FIV/ICSI results?

Numerous studies show that adenomyosis reduces the rate of implantation, the number of embryos transferred and the rate of pregnancy in patients following IVF cycles^(18,38). Other authors recommend screening for adenomyosis before starting assisted human reproduction procedures. The role of this recommendation is to be able advising patients about the prognosis of the procedure in the presence of adenomyosis. A recent study included nearly 1,000 patients who were divided into three groups depending on the presence or absence of adenomyosis and endometriosis. Clinical pregnancy rate has always been lower in the presence of adenomyosis. The rate of spontaneous abortion was 35% and 40% in adenomyosis patients compared with patients without pathology or in endometriosis patients without adenomyosis⁽⁴⁹⁾. A meta-analysis from 2017 showed the same result: the implantation rate, the pregnancy rate per cycle and per embryo transfer, and the live birth rate in women with adenomyosis are significantly lower than in women without adenomyosis⁽²²⁾. A. Hashimoto et al. emphasize that adenomyosis is associated with a higher risk of abortion in the second trimester of pregnancy, as well as a lower risk of adverse placental positioning⁽⁵⁰⁾.

Diagnosis and treatment of adenomyosis in infertile patients

Adenomyosis in infertile patients can be treated surgically or medically. Since effective therapeutic options are limited when it comes to preserving fertility in infertile patients with adenomyosis, we will only review the appropriate therapeutic options.

Surgical excision is indicated for patients seeking a pregnancy in case of focal adenomyosis or in the presence of adenomyomata. GnRH agonists (Gonadotropin-Releasing Hormone; GnRH_a) have a proliferative effect on tissues, induce apoptosis and reduce inflammation and angiogenesis⁽⁸⁾. Surgery in patients with adenomyosis and infertility should be considered in symptomatic women with repeated failure of implantation. Moreover, surgery increases the risk of uterine rupture⁽⁹⁾.

As mentioned before, focal adenomyosis can be excised more easily than diffuse adenomyosis which is more severe and more difficult to manage^(51,52). However, there are authors who support the effectiveness of surgery in treating diffuse adenomyosis⁽⁵²⁾. Instead of surgical treatment, the treatment with GnRH agonists is less invasive and easier⁽⁸⁾. The utility of GnRH agonists for adenomyosis, as well as their effect on fertility are suggested by numerous studies showing an increase in the rate of clinical pregnancies following embryo transfer with frozen embryos⁽⁵³⁻⁵⁶⁾. The treatment with GnRH agonists decreases the size of adenomyotic lesions and has a positive effect on implantation markers⁽⁵⁶⁾. In addition to the many advantages of using GnRH agonists, it seems that the disadvantages of using them are: higher doses of gonadotrophins required for ovarian stimulation and a higher number of stimulation days within IVF cycles⁽²²⁾.

Margit Dueholm and Jørn Aagaard recommend women with adenomyosis and repeated implantation failures to

address specialized centers for the treatment of adenomyosis or research⁽⁵⁷⁾.

What is the role of ultrasonography and MRI in the diagnosis of adenomyosis?

The diagnosis of adenomyosis in recent years can be determined both by transvaginal ultrasound and by MRI. Ultrasound diagnosis is possible with technological improvement. 3D (three-dimensional) ultrasound allows a more accurate assessment of the junctional area, as well as a precise description of certain features of adenomyosis⁽⁵⁸⁻⁶⁴⁾.

Adenomyosis is more and more common in women with infertility or subfertility, and both transvaginal ultrasound and MRI are non-invasive diagnostic tools similar in accuracy⁽¹⁹⁾. A meta-analysis from 2018 showed that 2D transvaginal ultrasound had a specificity of 63.9% and a sensitivity of 83.8% in the diagnosis of adenomyosis, while transvaginal 3D ultrasound had a specificity of 56% and a sensitivity of 88.9%⁽⁶²⁾. The Morphological Uterus Sonographic Assessment (MUSA) group developed in 2015 a system of uterine assessment criteria that allowed the diagnosis of adenomyosis to be made easier by certain standard characteristics: asymmetric thickening of the uterine wall, hypochoic intramural cysts or hypochoic islands tissue, the appearance of some shadows, sub-endometrial echoic lines, interruption of the junctional area etc.⁽⁶³⁾.

MRI assessment is considered as gold standard in the evaluation of adenomyosis⁽¹⁹⁾, but other authors show good correlation and good agreement between MRI and transvaginal ultrasound⁽⁵⁶⁾. Moreover, ultrasonography has the advantage of a lower cost and is more affordable than MRI⁽⁶⁶⁾. The diagnosis of adenomyosis by MRI is especially related to the thickening of the junctional area^(67,68). The most common features of adenomyosis seen in MRI, in addition to thickening of the junctional area, are: the presence of an enlarged asymmetric uterus, in the absence of uterine fibroids and high-intensity myometrial outbreaks in T1^(7,69,70). The MRI sensitivity in adenomyosis detection is 77% and the specificity is 89%, according to a recent study from 2018⁽⁷¹⁾.

What is the role of hysteroscopy in the diagnosis and the treatment of adenomyosis in infertile patients?

Currently, hysteroscopy is an indispensable diagnostic tool in the field of infertility. According to some authors, hysteroscopy is not a gold standard in assessing the uterine cavity in infertile patients before starting assisted human reproductive procedures⁽⁷²⁾. However, many infantile specialists do not start an IVF cycle without the patient having performed a diagnostic hysteroscopy⁽⁷³⁻⁷⁵⁾.

Starting with 2008, some studies support the use of hysteroscopy as a routine in evaluating infertility, as there is an increased incidence of intrauterine pathologies in infertile patients⁽⁷⁶⁾. Diagnostic hysteroscopy in asymptomatic women before the first IVF cycle is considered a safe procedure and has been associated with an increased chance of getting a pregnancy⁽⁷⁷⁾. Hysteroscopy allows the direct visualization of the uterine cavity. Hysteroscopy with

vaginoscopy allows the visualization of the uterine cavity in an atraumatic manner, without the need for a speculum that is difficult to tolerate for the patient^(78,79). The exploration of the uterus by hysteroscopy is limited to the uterine cavity and pathology associated with the endometrium. The exploration of the underlying myometrium can be done using the trophoscope that allows the extraction of endometrial biopsy⁽³¹⁾. Hysteroscopy exploration of the underlying myometrium may focus on the diagnosis of adenomyosis when there are specific signs such as neovascularization, endometriosis implants, or adenomyotic cysts⁽⁸⁰⁾.

Regarding the hysteroscopy diagnosis of adenomyosis, certain signs and aspects are suggestive: the irregular endometrium with small geodes, the accentuation of the vascularization, the "strawberry pattern" of the endometrium, the small fibrous cysts, the chocolate cysts that through transparency are colored in blue or brown-chocolate⁽⁸¹⁾.

Hysteroscopy treatment of adenomyosis is indicated in well-selected cases and in patients who desire to preserve fertility, and aims to remove adenomyotic tissue entirely without affecting healthy adjacent muscle tissue^(82,83).

Hysteroscopy allows the enucleation of focal or cystic adenomyosis by means of the bipolar strand. The technique is similar to the one used for hysteroscopy myomectomies (slicing), the difference being that in the case of adenomyosis there is no capsule showing the resection limit^(78,84). If the nodule is implanted deeper, the hydro massage technique by juggling with intra-cavity pressures leads to its migration closer to the cavity and easy access for resection⁽⁸⁵⁾.

Diffuse adenomyosis cannot benefit from hysteroscopy resection⁽⁸⁶⁾. In the case of diffuse superficial adenomyosis, the incisions of several millimeters can be made by means of the monopolar needle. This is a backup solution that is not documented and can be useful as a backup technique for patients with quality blastocysts and multiple implant failures where classic surgical methods and therapeutic methods have not proven effective.

Conclusions

Transvaginal ultrasound and MRI exploration are two non-invasive diagnostic tests and extremely useful in the diagnosis of adenomyosis, having similar sensitivity and specificity. Diagnostic hysteroscopy performed routinely in asymptomatic women before starting an *in vitro* fertilization cycle is associated with a higher pregnancy rate and a higher live births rates. The negative effect of adenomyosis on pregnancy rate in patients seeking a pregnancy and appealing to assisted human reproductive techniques is well known, and the use of the long-acting GnRH antagonist protocol appears to be beneficial in these patients. Hysteroscopy is a useful therapeutic and diagnostic method for infertile patients with adenomyosis, as many specialized studies show. Hysteroscopy is a useful method of diagnosis and treatment only in well-selected cases of cystic, focal and superficial diffuse adenomyosis. Exploring the uterus should not be limited to hysteroscopy in infertile patients with adenomyosis. ■

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