

Table of content

Abstract.....	2
1.0 ADENOMYOSIS.....	3
1.1 Definition.....	3
1.2 Pathophysiology.....	3
1.2.1 Contractility, gene expression and other factors.....	5
1.3 Symptoms and clinical features.....	5
1.4 Prevalence and etiology.....	6
1.5 Infertility.....	6
1.6 Risk factors.....	7
1.7 Associated disorders.....	7
2.0 DIAGNOSIS.....	9
2.1 Ultrasound.....	9
2.2 MRI.....	10
2.3 Cut off.....	11
2.4 Biopsy.....	11
3.0 TREATMENT	12
3.1 Medical therapy.....	12
3.1.1 Pain killers	12
3.1.2 Oral contraceptives	12
3.1.3 Gonadotropin-releasing hormone agonists, GnRHa	12
3.1.4 Levonorgestrel intrauterine system, Lng-IUD, MIRENA	13
3.1.5 Danazol	13
3.1.6 Aromatase inhibitors	13
3.2 Surgical treatment	14
3.2.1 Endometrial ablation and resection	14
3.2.2 Excision of the myometrium.....	14
3.2.3 Hysterectomy	14
3.3 Other treatment options.....	15
3.3.1 Uterine artery embolization	15
3.3.2 MRI-assisted high-intensity focused ultrasound ablation	15
References.....	16

Abstract

Adenomyosis is a common condition characterized by invasion of endometrium into the uterine muscle tissue. This results in myometrial hypertrophy and hyperplasia around the ectopic endometrial glands. The most frequent symptoms associated with the condition are dysmenorrhea, menometrorrhagia and chronic pelvic pain. Recently, infertility has been recognized as being a part of the clinical picture. Until recent years, adenomyosis has primarily been diagnosed in women who are in the late fertile or post fertile years of their life, and the reported prevalence rates varies widely, from 1% to 70%, depending on which population is studied and which diagnostic criteria are used.

Clinical diagnosis of adenomyosis is difficult because the signs and symptoms are unspecific. Historically, the diagnosis has been made on hysterectomy specimens. With the advance in medical technology the last few decades, new imaging techniques have been introduced. With transvaginal three-dimensional ultrasound (3D TVU) and magnetic resonance imaging (MRI) it is now possible to make a non-invasive diagnosis of the condition.

Treating adenomyosis is a challenge, and hysterectomy has been the only way to treat the condition effectively. There are, however, several alternative options available, such as various types of hormonal therapy, hormone releasing intrauterine devices and minimally invasive procedures that show promising results. A non-invasive diagnosis and treatment that does not require removal of the uterus is especially important for younger women with adenomyosis who wish to preserve their fertility.

1.0 ADENOMYOSIS

Adenomyosis is a common benign gynecological disorder amongst women in their reproductive years, that can cause an array of different symptoms (1). It is characterized by a chronically disrupted boundary between the endometrial basal layer and the myometrium, which leads to the invasion of endometrial glands into the myometrium, and the result is myometrial hypertrophy and hyperplasia caused by the ectopic endometrial glands (2).

1.1 Definition

The traditional definition of adenomyosis has been «the benign invasion of endometrium into the myometrium, producing a diffusely enlarged uterus which microscopically exhibits non-neoplastic endometrial glands and stroma surrounded by the hypertrophic and hyperplastic myometrium» (3). The definition of the disorder has continuously been changing during the last decade, as new technology has made it possible to visualize and investigate the underlying disease in a way that has not been available before (4).

The degree of invasion into the myometrium shows a great variability (1). There is no generally agreement upon the diagnostic criteria, and several classification systems and histological diagnostic criteria are currently being used. The data that exist are in general from women in their late fertile or post fertile age, but more recent research has shown that the phenomenon exists in young and adolescent women as well (5)(6)(7).

1.2 Pathophysiology

The hallmark finding in uterine adenomyosis is the chronic disruption of the boundary between the basal layer of the endometrium and the myometrium, known as the junctional zone (JZ), and the presence of endometrial glands and stroma within the myometrium. However, the underlying cause still remains unclear. The JZ has several distinctive properties, and the disruption of this zone is thought to contribute to the chronic pelvic pain associated with adenomyosis, as well as infertility, abnormal menstrual bleeding and the development of endometriosis (4). Other significant elements in the pathogenesis of the condition are hormonal, immunological, genetic and growth factors (8). The ectopic endometrial mucosa resembles non-secretory basal endometrium, and normally the posterior wall of the uterus is affected to a greater extent than other areas of the uterus (2).

A classification system has been suggested, which makes it possible to grade the adenomyosis according to the presence of adenomyotic lesions (>2,5mm from the JZ), depth of penetration of the

myometrium (A), degree of spread (B) and configuration of the lesion (C) (2):

(A) Depth of penetration:

1. *Mild disease* – involving the inner third of the myometrium
2. *Moderate disease* – involving two thirds of the myometrium
3. *Severe adenomyosis* – involving more than two thirds of the myometrium

(B) Degree of spread:

Grade I: 1-3 islets

Grade II: 4-10 islets

Grade III: >10 islets

(C) Configuration of the lesion:

a) *Diffuse adenomyosis*

Invasion of endometrial glands and/or stroma into the myometrium may be observed as islands of adenomyotic tissue spread diffusely throughout the uterine muscle tissue. Diffuse adenomyosis is the most common of the two types of the condition, and is found in approximately two thirds of the cases (9)(10).

b) *Focal adenomyosis*

This type of adenomyosis is also called nodular adenomyosis or adenomyoma (11). It is not seen as frequently as diffuse adenomyosis. More circumscribed infiltration in the uterine muscle is often observed in this group of patients. The adenomyotic lesions are normally discrete and well defined, or found as nodules within the uterine muscle (10).

Four theories for the etiology of adenomyosis have been proposed (12):

1: *Adenomyosis develops from the invagination of the endometrium into the myometrium*

There are a few different theories as to why the invagination occurs. It might happen because of previous trauma, which has caused weakened myometrium. It could also be due to an aberrant immune response in the affected tissue, as it has been shown that some antibodies produced by T and B cells can stimulate cytokines that may disrupt the endometrial JZ. The fact that the endometrium basale is quite similar to the adenomyotic nodules supports this theory (8). Newer theories have suggested altered uterine motility and contractility as a possible cause of the JZ disruption, but this has not been confirmed.

2: *Adenomyosis develops from embryologic misplaced pluripotent müllerian remnants*

This theory is supported by findings that showed that the eutopic and the ectopic endometrial tissue react differently to hormonal changes. Various growth factors and cytokines were also expressed differently in the adenomyotic tissue compared to the eutopic endometrium. This indicates that the

two types of tissues may have different biological characteristics, which could be explained by a difference in origin (12).

3: Adenomyosis is formed by the invagination of the basalis layer along the intramyometrial lymphatic system

This hypothesis is supported by the occasional findings of endometrial tissue in the intramyometrial lymphatics. It indicates that the lymphatic system within the myometrium is a possible route for the invagination of the basal endometrium. Isolated nodules of endometrial stromal cells without endometrial glands found along blood or lymphatic vessels can mean that new stroma may act as «new soil» for proliferative endometrial glands (8).

4: Adenomyosis originated from bone marrow stem cells that are misplaced throughout the vasculature

The fact that endometrial regeneration can be driven by bone marrow-derived stem cells supports the theory that states that adenomyosis may originate from stem cells. In four women who received single-antigen human leukocyte antigen (HLA) mismatched bone marrow transplants, the presence of donor endometrium glands and stroma was detected (12).

1.2.1 Contractility, gene expression and other factors

Experimental data from videasonography show altered myometrial contractility in endometriosis, and also uterine hyperperistalsis and dysperistalsis. And it is suggested that it could be connected to the pathogenesis of endometriosis (8)(13). Studies are not done on the same topic concerning adenomyosis, but as the two diseases are closely related, and share some of the same characteristics, suggesting that such a connection may exist between adenomyosis and uterine dysperistalsis as well. Some researchers have indicated that this type of dysperistalsis or hyperperistalsis could cause damage to and/or physical disruption of the endometrial-myometrial interface (8).

Some studies have shown an abnormal distribution of receptors in adenomyotic endometrium, as well abnormal cell density and nuclear size. Estradiol receptor expression is higher in the adenomyotic foci than in the normal endometrial tissue, which can indicate that the condition is, like endometriosis, probably estrogen-dependent. Various other soluble substances, like cytokines, growth factors and leukotrienes among others, have also shown deviation in the adenomyotic tissue, compared to normal cells (5)(12)(14)(15).

1.3 Symptoms and clinical features

The clinical presentation can be very variable, and the diagnosis is most often made in women in their forties and fifties (1)(12). Women with adenomyosis most commonly have dysmenorrhea and

menometrorrhagia, and chronic pelvic pain (16). Dyspareunia is observed in some of the patients, and they may have an enlarged and tender uterus upon examination (9).

Clinical diagnosis of adenomyosis is very difficult because the signs and symptoms are nonspecific. In for example endometriosis, dysfunctional uterine bleeding and fibroids, many of the same clinical features will be present (2)(9)(10). Many women being diagnosed with adenomyosis do not have the symptom complex described above, and some studies show no clear correlation between symptoms and the degree of pathology, while others show a clear correlation (1). As many as 30%-50% of women with adenomyosis are asymptomatic, and the diagnosis is most frequently made histologically when other types of pelvic pathology results in hysterectomy (10)(17).

1.4 Prevalence and etiology

The reported prevalence shows a great variation depending on which diagnostic criteria are used and which population is being studied. Earlier the diagnosis was only made from histological samples, and because most women that have a hysterectomy are in their forties and fifties, the material available for research was not representable for the general population (5)(7). Numbers ranging from 1% up to 70% are described, but according to two different systematic reviews done in 2006, the prevalence is thought to be 20%-30% in the general female population (5)(6)(7). The prevalence amongst women with bleeding disorders is estimated to be closer to 50% (2).

1.5 Infertility

Infertility is also being recognized as part of the symptom complex, and this is partly because more and more women choose to delay their first pregnancy until their late thirties or early forties. This makes adenomyosis more relevant in the context of subfertility (1)(18). Historically, adenomyosis was thought to be a disease of multiparity and not infertility.

Most studies show that women undergoing hysterectomy are in their later reproductive years and have already had children. This results in a lack of information about the disease in its earlier stages, as most of the data that exists are from the hysterectomy specimens (6)(7)(19).

When investigating women who struggle with infertility, adenomyosis is a frequent finding. The available data on the topic suggest that the presence of adenomyosis has a negative effect on female fertility. In the presence of both endometriosis and adenomyosis the fertility is even lower (20). A review article from 2012, that reviews six studies, established that adenomyosis can affect the outcome of in vitro fertilization (IVF) treatment negatively, and that infertility can be added to the

list of symptoms that are associated with adenomyosis (20).

The aspects that are linked to infertility are:

1. Impairment of the uterine mechanism of sperm transport, possibly due to the destruction of the normal architecture of the myometrium.
2. The abnormal peristalsis of the myometrium in adenomyosis could also be a contributing factor to the reduced rate of implantation following IVF treatment.
3. Women with adenomyosis have a different endometrial environment compared to fertile women, with an abnormal immune status, and abnormal immune responses that are thought to trigger events that may impair implantation.

Several of the studies that exist now conclude that more studies are needed to be certain about the true impact of adenomyosis on fertility. Indications are that it can definitively be a contributing factor to infertility in this group of patients. With the advantages made in imaging modalities and preoperative diagnostics, it is possible to find out more about what is the best treatment for women with infertility and symptoms of adenomyosis, and to improve their chances of pregnancy. There is a need to assess the different treatment options as to how effective they are, not only to relieve symptoms, but also to improve fertility (7)(20).

1.6 Risk factors

Some evidence points to a familial predisposition. Studies suggest that nearly all cases of adenomyosis occur in multiparous women, and therefore high parity has been thought to be a risk factor. Now it is considered a consequence of the material originating from women who are relatively older, and have already completed having children (8). It is a more common understanding now, that the condition is more closely related to an increased difficulty for the women to become pregnant.

One could imagine that any procedure or condition that disturbs the endometrial-myometrial junction can be a contributing factor to the adenomyosis, although some studies have found no significant correlation between caesarean section, endometrial curettage or evacuation (21).

1.7 Associated disorders

Several studies show that in a majority of the cases adenomyosis coexists with another pelvic pathology. It is suggested a rate as high as 80% (19). The most commonly associated pelvic pathologies in women with adenomyosis are fibroids and endometriosis. Fibroids are found in 35%

to 55% of the patients in this group (10). This can make it more difficult to interpret the findings on MRI and 3D TVU, and therefore more difficult to be certain of the diagnosis.

Pelvic endometriosis coexists with adenomyosis in 2%-24% of the cases, which some studies interpret as a suggestion that the two conditions are linked or variants of the same disease (5)(17). In women with endometriosis, 27% had concomitant adenomyosis (8). It is greatly debated how closely linked the two conditions are, but the common understanding is that the two diseases have the same «target tissue» for treatment, ectopic endometrium, and that they are both estrogen-dependent conditions (5)(11).

2.0 DIAGNOSIS

Usually a doctor will suspect that a woman has adenomyosis from her symptoms and her medical history. Clinical investigation can sometimes reveal a uterus that is tender upon examination, and it may be enlarged and/or have a more doughy consistency upon palpation compared to a normal uterus, which could feel more firm and elastic (22).

For more than a century, the primary diagnostic tool and most effective treatment option have been hysterectomy (23). Because of the advancement made in medical technology, doctors now have more alternatives when it comes to less invasive options, both in diagnostic tools and therapeutic methods. In the late seventies gray-scale ultrasound was used, but in the mid-eighties a significant advance came with the introduction of MRI and transvaginal ultrasound (TVU) (8). Several studies suggest that both ultrasound and MRI are able to provide a non-invasive preoperative diagnosis. They both have a high accuracy, and several studies have found comparable accuracy between TVU and MRI (6)(8)(9)(11)(24). One important differentiation that should be made, is to exclude leiomyomas, as the treatment approach is different (25).

The correct diagnosis of this condition at a younger age can be very beneficial for a large group of women. It will be especially beneficial for those with unexplainable pelvic pain and for patients with adenomyosis for whom extensive surgery is not an option, or at least considered as the last resort. With TVU and MRI, this is possible. In several studies MRI was found to have a sensibility of between 86%-100% and a specificity of 67%-93%, with an accuracy of 85%-90,5%. 3D TVU had an sensibility of 80%-88% and a specificity of 50%-95%, and the accuracy was found to be 68%-86% (11)(22)(25)(26).

2.1 Ultrasound

Ultrasound will often be the first step in the process of diagnosing adenomyosis. Ultrasound equipment is usually widely available in gynaecologists' offices, and it has the advantage of being much less expensive and more time efficient than the MRI procedure (4)(6). A problem with this method is that it is highly observer dependent, and it is difficult to reproduce the results.

Transabdominal ultrasound was previously used, but is now not considered as good as TVU, and it is rarely used for this group of patients. Two-dimensional ultrasound was also used in the beginning, but is discarded as the 3D ultrasound came along, as it proved to be much more reliable.

Early use of TVU to evaluate the potential existence of adenomyosis can be an important part of

being able to guide the patient in their choice of treatment options and their future fertility (4). Adenomyosis appears as heterogeneous and hypoechogenic poorly defined areas in the myometrium on TVU (8).

Sonographical findings that can justify an adenomyosis diagnosis are:

1. A globular uterine configuration
2. Poor definition of the endometrial-myometrial interface
3. Subendometrial echogenic linear striation
4. Myometrial anterior-posterior asymmetry
5. Intramyometrial cysts
6. A heterogeneous myometrial echo texture

According to a study on the sonographical features of adenomyosis, the most specific finding on ultrasound was the presence of subendometrial linear striations (95,5%), which also had the highest positive predictive value (80,0%) (11).

3D TVU offers increased visibility of the uterus, and enables the operator to see lateral and fundal aspects of the JZ. The high accuracy of this procedure is comparable with MRI as a diagnostic tool for adenomyosis. The most reliable markers are related to the JZ, and the results are relatively more accurate than regular 2D TVU (4)(8). JZ increases in thickness from the early proliferative to the late secretory phase (8). A normal JZ is between 5 and 12 mm thick on T2-weighted MRI. In the luteal phase of the menstrual cycle, the 3D TVU is much more reliable than the 2D US.

2.2 MRI

The JZ of the uterus is well demonstrated on T2-weighted MRI images. Features that are highly predictive of the presence of adenomyosis includes a JZ measuring >12mm and hemorrhagic high signal myometrial spots (8). In the presence of a uterine leiomyoma, the MRI perform more favourable than the TVU, both in identifying the adenomyotic lesions and in localizing and enumerating the leiomyomas. This is helpful when planning what type of surgical treatment could be appropriate. In addition, there is more inter-observer agreement when using MRI than when using TVU (9)(26). A downside of using MR imaging as a diagnostic tool is that it is a high cost examination, the procedure takes a lot of time and the patient usually has to wait a long time before getting an appointment.

More specifically, on MRI scans one can usually find a large asymmetric uterus without

leiomyomas, and diffuse or focal thickening of the JZ from 8 to 12 mm due to hyperplasia and hypertrophy (12).

Three objective parameters have been identified for diagnosing adenomyosis on MRI:

1. Thickening of the JZ ≥ 12 mm
2. A ratio of maximum thickness of the JZ (JZmax)/total maximum myometrial thickness $> 40\%$
3. A difference between JZmax and JZmin (maximum thickness of JZ – minimum thickness of JZ = JZ difference) > 5 mm.

The first two criteria are criticized because if they are not accurate enough due to their dependence on hormonal status and menstrual cycle. The third criteria is thought to be more trustworthy in this regard (4)(24).

2.3 Cut off

There is no generally agreed upon cut off limit for diagnosing adenomyosis, and diagnostic criteria and cut off point for the diagnosis are still controversial (8)(11). One of the main reasons for this is the fact that some irregularity in the endometrial-myometrial interface is considered common and can occasionally be observed in women without uterine adenomyosis or other pelvic pathology (8). Usually one will find a range of different data, at least concerning prevalence, depending on what criteria are used for the diagnosis. Many studies emphasize this, suggesting that more studies should be done, and an agreement on the diagnostic criteria should be made (7).

The last 15 years, many researchers have advocated that adenomyosis should be diagnosed when the distance between the lower border of the endometrium and the affected myometrial area is over one half of a low-power field, or approximately 2,5mm. Obviously, the choice of «minimal depth of invasion» will have a great effect on the reported frequency of adenomyosis (19).

2.4 Biopsy

Methods for taking needle biopsies have been developed and are being used to some extent, but not as a routine. In 2003, a TVU-guided biopsy of the uterus was introduced. In a study performed with 100 patients with symptoms suggesting adenomyosis, laparoscopy-guided myometrial biopsies reported 98% sensitivity, 100% specificity and 100% positive and 80% negative predictive value (8) (27). In another study, the preliminary ultrasound diagnosis was confirmed histologically in 36,4% of the patients after biopsies were examined. The more biopsies taken from each patient, the more accurate the diagnosis (27).

3.0 TREATMENT

No general agreement exists as to what is the most appropriate therapeutic method for managing women with uterine adenomyosis who wish to preserve their fertility.

Hormonal treatment aims to reduce the proliferation of endometrial cells and relieve symptoms caused by the hyperestrogenic state. Many women experience relapse of the disease and reappearance of symptoms when stopping or interrupting suppressive hormonal treatment (11). There are few studies with good documentation and none that give reasonable guidelines for treatment, therefore these studies often conclude that more research is needed. However, many of the studies are promising (7)(28).

3.1 Medical therapy

3.1.1 Pain killers

Normally painkillers are the first step in the conservative approach. The most frequently used painkillers are anti-inflammatory drugs such as ibuprofen, or other kinds of non-steroid anti-inflammatory drugs. The mechanism of action in these drugs is related to the inhibition of enzymes, the cyclooxygenases (COX), which amongst other things synthesizes prostaglandins, known to contribute to pain.

3.1.2 Oral contraceptives

Oral hormonal contraceptives have been shown to have several non-contraceptive benefits, especially in treating menstrual-related pain symptoms. Combined oral contraceptives or progestin-only oral contraceptives are both options, and some doctors recommend continuous use of oral contraceptives when treating adenomyosis. This can benefit some patients, as it will induce amenorrhea, which can relieve the symptoms (12). Some studies suggest that oral contraceptives have a similar effect to the Gonadotropin-releasing hormone agonists (GnRHa) used as treatment for pain symptoms in adenomyosis and endometriosis, and it is a less expensive treatment, with less side effects. It is also a benefit that these contraceptive drugs can be used for a longer period of time (29).

3.1.3 Gonadotropin-releasing hormone agonists, GnRHa

These agonists binds to receptors in the pituitary gland, and by doing so it down-regulates GnRH activity. In a way it induces menopause, but the state is reversible (12). The drug has been used in several studies and has shown to reduce pain, reduce uterine size and can lead to amenorrhea due to a more or less constant hypoestrogenic state (11)(28). The GnRH agonists are highly effective, but

are not suitable for long-term use because of the hypoestrogenic side effects. Treatment for 3-6 months is normal and have been followed by viable pregnancies. The treatment can be indicated for women with diffuse disease, who wants to conceive after treatment. Pre-operative use in patients with nodular disease is also indicated, to make the nodules reduce in volume and vascularization (11).

3.1.4 Levonorgestrel intrauterine system, Lng-IUD, MIRENA

This small device is inserted in the uterus, and is normally used as a contraceptive. When adding progesterone to these devices they can be used to treat menstrual disorders. Hormone releasing IUDs may relieve the symptoms of adenomyosis quite effectively (1)(11)(30). The mechanisms of action that can explain the effect against the symptomatology in adenomyosis are: decidualization of the endometrium and atrophic changes which leads to a significant reduction in menstrual blood loss (1). Estrogen receptors are down-regulated both in glandular and stromal endometrial tissues, and this can cause the adenomyotic deposits to reduce in size, which in turn can lead to a shrinkage of the uterus and improved contractability (12). Dysmenhorrea can also be improved due to a reduction of the prostaglandin production in the endometrium (1). It is currently not known whether LNG-IUD is useful in treating infertile patients who want to conceive after treatment (12)(31). A disadvantage with this treatment is that many patients experience intermenstrual bleeding, spotting and irregular bleeding, especially during the first months of treatment.

3.1.5 Danazol

There exists limited data on the use of Danazol in the treatment of adenomyosis, but this drug works by inducing a hypogonadic state, inhibits ovarian estrogen production, prevents ovulation and interacts directly with endometrial receptors for androgens and progesterone. The endometrium will become atrophic, and some reduction in estrogen receptor has been observed (11). Many of the patients will experience a recurrence after a few month when stopping the treatment. Long-term treatment is not recommended, partly due to the androgenic side effects like hirsutism, weight gain, acne and deepening of the voice. There has also been developed an IUD releasing Danazol which shows promising results, but it is not used (11)(12).

3.1.6 Aromatase inhibitors

This treatment is based on the consideration that both adenomyosis and endometriosis are conditions that are estrogen dependent, and that many of the treatments used for endometriosis have been shown to have an effect on adenomyosis as well. The drug inhibits an enzyme that converts androgens into estrogens. The enzyme, aromatase, is found in the endometrium of women with

endometriosis, adenomyosis and leiomyoma (11)(12). The aromatase inhibitors are shown to be as effective as gonadotropin releasing hormone agonists (GnRHa) in reducing adenomyoma volume and improving the women's symptoms (28). It has been used post-operatively in combination with a GnRHa to reduce the recurrence risk after conservative surgery, and also reduce the symptoms (1) (30).

3.2 Surgical treatment

Based on the woman's age, fertility desire in the future, the size and the extent of the adenomyotic lesions and the surgeon's preference and skill, a surgical approach can be decided.

3.2.1 Endometrial ablation and resection

This surgical intervention removes the inner lining of the uterus and has been used to treat menorrhagia. It can be used to treat superficial adenomyotic lesions, but has been shown to have limited utility if there are deeper lesions present. The depth of penetration is not always known at the time of ablation, and the depth is correlated with the success of resection. If one is not able to remove all the lesions, the symptoms are more likely to recur after treatment. Also, risk of bleeding is significantly higher with deeper lesion resection (10)(12).

3.2.2 Excision of the myometrium

Excision of adenomyosis is possible if the location of the lesion can be determined. The efficiency of excision in one study was 50%. This is related to the fact that adenomyotic lesions may be difficult to expose in the myometrium, and the margins between sick and healthy tissue may not be easily defined. A scar will form in the uterus, and this could have an impact on the woman's ability to bear children, by interfering with uterine expansion (12).

3.2.3 Hysterectomy

This is the only proven treatment and also the only way to get a definite diagnosis. Both abdominal and vaginal hysterectomies are options, but vaginal hysterectomy is preferred to the abdominal procedure, as it is shown to have fewer complications and a faster recovery. If the abdominal procedure is performed, usually surgeons prefer the minimally invasive laparoscopic approach to the laparotomy (10)(12)(23). Hysterectomy is the treatment of choice in women who have no desire to conserve their fertility, but also in women with severe adenomyosis where less invasive treatment options have not been successful (10).

3.3 Other treatment options

3.3.1 Uterine artery embolization

This is an option for patients who do not wish, or are not suitable for surgical procedures (23). Some studies show limited long-term effectiveness, and it has been reported an age-related impairment of ovarian function following uterine artery embolization, which may lead to amenorrhea. This treatment does not rule out the possibility of later pregnancies, but can involve a higher risk of abnormal placentation and therefore more complications (10)(31).

3.3.2 MRI-assisted high-intensity focused ultrasound ablation

This treatment can be effective in patients with localized disease, and some studies done in China showed an advantage over current conservative treatments (7)(31). A recent asian study showed that this treatment was effective in both focal and diffuse adenomyosis, and could alleviate the symptoms of menorrhagia and dysmenorrhea. The overall efficiency though, was higher in patients with focal disease (32). As the treatment is very time consuming is a disadvantage, and the treatment is not widely used.

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