Chapter

Uterine Embolization as a New Treatment Option in Adenomyosis Uteri

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Abstract

Adenomyosis is characterized by the development of endometrial ectopic glands and tissue in the myometrium layer in depth greater than 2.5 mm from the endometrial surface of the separative area by -myomas well as by hypertrophy and hyperplasia of the smooth muscles of the myometrium. This is filtration, not mere displacement, of the myometrium, from the endometrium. Clinical symptoms include dysmenorrhea and menorrhagia. It is diffuse (adenomyosis) or focal (adenomyoma), asymmetrically affects the uterine wall of premenopausal women (usually the posterior) and often coexists with myomas. The pathogenesis of adenomyosis remains unknown. The treatment options are: drug therapy, invasive treatment of fibroids: myomectomy (open—intra-abdominal, laparoscopic, hysteroscopic), hysterectomy, myolysis—cryocatalysis, microwave or radiofrequency thermal catalysis (RF-ablation), ultrasound focus catalysis (FUS), laser photocatalysis and percutaneous selective uterine artery embolization (UAE). Embolization remains an alternative and not a substitute of hysterectomy. The medical indication is made on a case-by-case basis, depending on age, desire for pregnancy and the clinical symptoms of adenomyosis.

Keywords: adenomyosis, adenomyoma, uterine artery embolization, conservative therapy, surgical procedures

1. Introduction

Adenomyosis consists of a term that describes the presence of endometrial glands in a layer deep in the myometrium, in a random arrangement and similar histological lesions can be also appeared outside of the uterus, such as the area of the rectal septum [1–3]. Pathogenesis and etiology of adenomyosis development have not been elucidated thoroughly.

Studies in humans and experiments in animals support the hypothesis of endometrial insertion from the myometrium, although the development of adenomyosis from Müller's duct debris at locations outside the uterus is possible from the outset.

The conditions for the development of adenomyosis can be either some "weakness" of the smooth muscle fibers of the myometrium or the increased pressure in the uterine cavity or both. To maintain adenomyosis, relatively high concentrations of estrogen and impaired control of the development of the ectopic endometrium, which is associated with the immune system, may be necessary. Hyperplasia and hypertrophy of smooth muscle fibers are a reflection of the reactive changes in the proliferation of ectopic endometrium. The definitive diagnosis is made after hysterectomy, although efforts have been made to confirm the diagnosis preoperatively with magnetic resonance imaging and endometrial biopsies [4–6].

1.1 Genetic predisposition

Adenomyosis, one of the most common diseases in gynecology with a frequency ranging between 5% and 70%, can significantly affect the quality of life of women with clinical symptoms such as menorrhagia, dysmenorrhea and infertility [7–9]. There are two prevailing theories concerning the origin of adenomyosis. One supports "migration", which concerns the penetration of the endometrium into the myometrium, while the other is based on the metaplastic differentiation of the remaining endometrial stem cells in the myometrium. Mutations that have been observed, almost exclusively, in the KRAS genes, in the presence of adenomyosis, underscore the importance of these genes in the pathogenesis of the disease at the genetic level. This discovery of the cause-effect relationship between the presence of mutations in the aforementioned [7–9] KRAS genes and adenomyosis refuted the recent theory that the reported molecular abnormalities in adenomyosis are mainly epigenetic or associated with abnormal expression in different genes [7–9]. Most recognized abnormalities regarding gene expression, were associated with excess estrogen formation, progesterone resistance and were related to steroid hormone receptors and other transcription factors. More specifically, mutations have been found, such as the following two P129R, M427I/L429M, which are the most predominant ones, in the ESR1 gene of the estrogen receptor α (ERa) located on chromosome 6q25.1 and appear to be involved in the etiology of adenomyosis [7–9]. It has also been described an association between adenomyosis and deregulation of mechanisms involved in the transition process of epithelial to mesenchymal cells, as occurs in cases of decreased expression of Cadherin-1 (CDH1) protein, as well as in cases of increased Notch I and TGF-β levels [7–9]. Regarding epigenetic factors, it has been suggested that Class I histone deacetylases (HDACs) are involved in promoting gene transcription, as well as DNA methyltransferase (DNMT) proteins involved in DNA methylation are associated with adenomyosis. High levels of HDAC1 and HDAC3 as well as DNMT1 and DNMT3B were found in cases of adenomyosis at the ectopic endometrium. Consequently, epigenetic alterations seem to play an important role in the pathogenesis of adenomyosis, which along with the other aforementioned genetic factors provides knowledge that could potentially lead to advances in the diagnosis and treatment of the disease [7–9].

1.2 History of adenomyosis

In the mid-nineteenth century, Rokitansky described a condition in which elongated endometrial glands were embedded in the hyperplastic endometrial layer. The author mentioned two variants of this condition: the first, in which the glands developed in the muscular wall of the uterus and the second, in which the glands extended to the intrauterine cavity, forming polyps [10]. Several researchers in the 1880s and 1890s considered adenomyosis to be either an embryonic error in the distribution of Müller's ducts or the penetration of the hyperplastic basal endometrium into the myometrium [10–14]. Von Recklinghausen, then argued that adenomyosis is the result of displacement of the mesonephric elements. The researcher reported that these ectopic glands are more commonly found in the posterior wall of the uterus and the area of the cornea, and that these areas consist of remnants of Wolff's pores rather than Müller's ducts [10–14]. Marcus, later described the lymphatic transmission of endometrial elements [14]. Although, this theory has been used to interpret pelvic endometriosis, it also provides a possible explanation for adenomyosis. Marcus, then suggested that there are some miller pluripotent cells in the myometrium, which can differentiate into endometrial cells, offering another possible interpretation for the development of adenomyosis [14]. The cycle is now complete, and most researchers believe that adenomyosis is caused by the penetration of the basic endometrium into the hyperplastic layer of the myometrium. It should be noted that all the organs of the human body, which show cavities, present a sub-orogenic area, except for the uterus. It is believed that the main function of the sub-orogenic region is to inhibit the growth of the glands that line these cavities. The term "uterine adenomyosis" was first used by Frankl in 1925. In 1972 Bird and his colleagues defined adenomyosis as "benign, penetration of the endometrium into the myometrium, which causes diffuse enlargement of the uterus and microscopically presents ectopic, non-neoplastic, endometrial glands and layer, surrounded by hypertrophic and hyperplastic endometrium" [15]. This definition still applies today.

However, it has been described by some researchers as "the presence of endometrial glands and a layer, which are diffuse and deep inside the myometrium". The issue of depth is important as the normal endometrial contribution is usually irregular. Thus, adenomyosis must be distinguished from cases in which there is minimal adhesion of the basal layer of the endometrium surrounded by myometrium and there are two ways to treat it. The first case is the detection of myometrial hypertrophy ("collar around the foci of adenomyosis"), because this type of change is not observed in the intramuscular junction. The second way is to measure the distance between the endomyometrial junction and the nearest adenomyotic site, the size of which must correspond to at least 25% of the total thickness of the myometrium. The second approach is particularly useful in the postmenopausal and pregnant uterus, as in these cases there is generally no muscle hypertrophy around the foci of adenomyosis. Although, many researchers consider adenomyosis as a variety of endometriosis and call it internal endometriosis, adenomyosis should be defined as the presence of endometrial glands and mattresses, located outside the myometrium [10–18].

1.3 Epidemiology

The incidence of adenomyosis varies widely, with rates ranging from 5.7% to 69.6% [19, 20]. Although, some of this discrepancy can be explained by the different histological definitions of adenomyosis, the difference is mainly due to the interest of pathological volumes in making the diagnosis. As a result of the local entity of the condition, the diagnosis of adenomyosis is particularly difficult. In the excellent prospective study by Bird et al. [15], 200 consecutive hysterectomy

specimens were examined histologically. When three sections of the myometrium were examined, adenomyosis was found in 62 women (31%). When six more incisions were made, three from the anterior and three from the posterior wall of the uterus, another 61 cases of adenomyosis were diagnosed, increasing the rate from 31 to 61.5% [21–25].

The main reason for the difficulty in determining the true incidence of adenomyosis is mainly due to the fact that published studies report the number of adenomyosis cases, but without mentioning the total number of hysterectomies per age group, so the relative impact of adenomyosis with age has not been defined. Another problem is determining the true frequency is also the fact that in the various studies, only women who undergo a hysterectomy are evaluated, and a selection of cases is applied. In two necropsy studies, the incidence of adenomyosis was reported between 50 and 53.7% [21–25]. Although, these studies had a different choice of cases (excluding women who underwent hysterectomy), they show that the true incidence of adenomyosis is at the highest end of the published frequency range. The woman's interest appears to be related to adenomyosis, as 93% of the women treated had children [21–25]. Although, the numbers tend to mimic the general population, their importance is questionable. If these numbers are real, the observation will confirm an interesting paradox, that is, the number of pregnancies protects against endometriosis, but it is a risk factor for the development of adenomyosis. There does not appear to be a significant association between adenomyosis and another gynecological entity. In a retrospective study of 134 women who underwent a hysterectomy, Vercillini and colleagues found a similar coexistence of adenomyosis with fibroids (23%), with uterine prolapse (19%), with endometrial cancer (28%), with ovarian cancer (28%) and with ovarian cysts (21%) [26].

1.4 Pathogenesis

Although, the exact etiological factors of endometriosis have not been clarified yet, there are many theories on this subject, such as the ones proposed by Ridley [27]. According to the most popular view, adenomyosis is the result of the attachment of the basal layer of the endometrium to the myometrium. In non-uterine areas, the predominant theory concerning the pathogenesis of adenomyosis is the de novo development of ectopic fetal residues of Müller's ducts, since an invasive mechanism of the endometrium into the myometrium has not been established. There are significant differences in the cellular level between the basal layer of the endometrium and the functional layer, such as increased DNA synthesis in the nucleus, and margin formation in the functional layer. In general, the functional layer is considered to be the site of blastocyst implantation while the basal layer provides the possibility of intrauterine regeneration after menstruation. During the period of regeneration of the endometrium, cells from the basal layer glands are in close contact with the endothelial cells having intracellular microfiber/tubular and squamous cell systems [28–30].

These findings support the location of possible migration through amoebic contraction-extension. Such morphological changes have not yet been described in the intrauterine epithelium of adenomyosis. However, in vitro studies have shown that endometrial cells have the penetrating capacity and that their penetration rate is similar to that of cell lines from metastatic bladder carcinoma. This penetrating ability can facilitate the expansion of the basal layer of the endometrium to the myometrium. In MCF-7 cells from breast cancer, tenascin production is stimulated by epidermal growth factors (EGF), which are regulated by hormones. The fact that fibroblasts of the endometrial layer produce tenascine, a fibronectin inhibitor that in turn facilitates the migration of epithelial cells, suggests that there is a complex

physicochemical relationship during the growth process of the endometrium in the production phase. Tenascin has been immunohistochemically located around the endometrial glands during the productive phase of the cycle, but not in this position after ovulation [28–30]. Tenascin may mediate the interactions between epithelial and mesenchymal cells, where it inhibits cell adhesion to fibronectin in the endometrial adenomyotic type in the same way as in the normal endometrium.

In a study within situ hybridization and immunohistochemistry, it was found that the endometrial glands in adenomyosis selectively express more human chorionic gonadotropin (hCG) receptor mRNA and immunoreactive receptor protein, compared to the present [31–34]. It seems that HCG/LH receptor expression levels do not differ at different sites of the normal endometrium, but increased expression of this receptor may give epithelial cells the ability to invade the myometrium and form adenomyotic islets. Furthermore, quite interesting is the fact that there is an increased expression of hCG/LH receptors in endometrial carcinomas as well as in non-invasive choriocarcinoma trophoblast cells [31–34]. Studies on steroid hormone receptors in adenomyosis foci have shown dubious results. Thus, some studies reported the absence of progesterone receptors in 40% of adenomyosis cases, while others showed higher concentrations of progesterone receptors than estrogens. Relatively high concentrations of estrogen and progesterone receptors were found in both the basal and adenomyotic endometrium using immunohistochemical detection techniques. Estrogen receptors are a prerequisite for the development of the uterus, which is caused by estrogen [35–38]. Although, there is no clear evidence of a disturbed hormonal environment in most women with adenomyosis, hyperestrogenemia may play a role in the process of endometrial infiltration, as women with adenomyosis have a high rate of endometrial hyperplasia. According to some researchers, a relatively high concentration of estrogen is necessary for the development of both endometriosis and adenomyosis [31–38]. The clinical observation that the destruction of the estrogenic environment with danatrol causes regression of the ectopic endometrium and remission of the associated symptoms of menorrhagia and dysmenorrhea reinforces this hypothesis [31–38]. As in uterine fibroids, estrogen is synthesized and secreted in adenomyotic tissues [31–38]. It was found, therefore, that there is aromatase activity of estrogen sulfatase in the upper part of the myometrium, which contained foci of adenomyosis, by the method of steroid biochemical analysis. The activity of estrogen sulfatase and, in particular, aromatase was higher than that observed in normal adjacent endometrium, leiomyomas and suprauterine endometrium. In addition, endometrial aromatase enzyme activity was inhibited in vitro by up to 50% with the addition of 106 M of danatrol [31–38]. Finally, the presence of aromatase was confirmed in foci of adenomyosis from human matrices by immunohistochemical method and, in particular, in the cytoplasm of glandular epithelial cells, but not in the cytoplasm of stratum cells. The production of estrogen by adenomyotic tissue is further enhanced by the finding of a large number of women with adenomyosis and a high concentration of estradiol (30 pg/ml) in menstrual material compared to those without adenomyosis and normal menstrual cycles [31–38].

Adenomyotic tissue appears to respond well to progesterone with secretory differentiation. Progestogens also enhance aromatase activity in both eutopic endometrium and adenomyotic tissues, thus contributing to the biosynthesis of estrogen in adenomyotic foci.

It is possible, however, that the bioavailability of race steroids alone is not sufficient to develop adenomyosis. It is possible that the myometrium, in cases of adenomyosis, is either predisposed to penetrate the main endometrium, so that benign "penetration" of the endometrium occurs secondarily due to "weak" myometrium, or the morbidity of the uterine scraping, fibromyectomy and cesarean section. Thus,

adenomyosis was induced in pregnant rabbits, after scraping one horn of the uterus and fallopian tube, while maintaining the pregnancy in the opposite horn [31–38]. Penetration into the myometrium of the basal layer of the endometrium is enhanced, possibly, by increased intrauterine pressure, which, according to Cullen, can be caused by high circulating progesterone concentrations. The immunohistochemical method has been observed, increased expression of class II antigens of the major histocompatibility complex (HLA-DR) in the glandular cells of the idiopathic endometrium, endometriosis and adenomyosis [31–38]. In addition, the number of macrophages in the myometrium of women with adenomyosis appears to be increased. These macrophages can activate helper T- and B-cells to produce antibodies [31–38]. Phospholipid autoantibodies and significant deposition of immunoglobulins (lgs) or complement factors have been found in women with endometriosis or adenomyosis [31–38]. The exact importance of these immune aberrations in adenomyosis or endometriosis is not currently understood. In vitro experiments have shown that activated CD3+ T cells in the uterus and their secretory product, interferon γ, promote the expression of HLA-DR immunoreactivity in endometrial glandular cells and inhibit their proliferation [31–38]. The closer the endometrial cells are to the activated T cells, the greater the inhibition of their growth. It appears that lymphocyte-like formations, located mainly at the endomyometrial junction, are rich in activated T cells. Their appearance coincides with the maximum suppression of endometrial growth, which is observed both morphologically and with proliferation indices [31–38]. On the contrary, the proliferation of the endometrium is observed, to the greatest extent, near the surface of the endometrium, that is, far enough away from the basal layer, in which these lymphoid formations are found [31–38].

1.5 Pathological anatomy

During a hysterectomy, the adenomyotic uterus is usually spherical or soft. It is swollen in 60% of cases, but rarely exceeds the size of a 12-week pregnant uterus [39]. The uterus weighs from 80 to 200 g. In his classic study, in which a woman's interest determined the weight of the uterus, Langlois reported the upper limit of the normal uterus weight at 130 g for the unmarried woman, at 210 g for the firstborn to the third child, and at 250 g for women with four or more children [40]. With these criteria, excluding cases of fibroids, the weight of the uterus does not increase significantly with adenomyosis. Uterines with adenomyosis are usually hyperemic with thick walls. Although, many researchers have reported that adenomyosis is more common in the posterior wall of the uterus than in the anterior. Bird and colleagues found that the foci of adenomyosis were evenly distributed when receiving six additional incisions for histopathology [15]. These foci may be diffusely dispersed in the myometrium, and may sometimes be large and localized, forming structures called adenomas. The characteristic macroscopic appearance of adenomyosis is due to hypertrophy of the myometrium, which surrounds the endometrium [40–44]. When the entire myometrium, or one of the layers of the uterine wall, is diffusely affected, the uterus increases in size and takes on a spherical shape. During the cross-section of the uterus, the hypertrophic muscular beams are visible, which develop in all directions and surround the foci of adenomyosis. The latter, in some cases, may contain "old" blood with a brown appearance, corresponding to hemolyzed blood and hemosiderin deposits [40–44].

Local infection of the uterus by adenomyosis resembles fibroid. The term adenomyoma is used for the frequent occurrence of adenomyosis. Because the treatment is not neoplastic, the term focal adenomyosis is preferred by Hendrickson and Kempson [40–44]. As adenomyoma is often confused clinically with leiomyoma, which is a benign but neoplastic condition, the term adenoma is accepted. Typically

the adenoma does not have clearly defined boundaries because they merge with the normal myometrial environment. In contrast, leiomyomas compress the myometrial environment and have well-defined boundaries [45–50].

Leiomyoma can be nucleated, while adenomyoma can not. Histologically, by the immunohistochemical method, the endometrial glands and the layer in foci of adenomyosis resemble the basal layer of the endometrium. Rarely do they respond to hormonal stimuli, a phenomenon that explains, at least in part, that only in certain cases are hemorrhagic or regenerative morphological findings observed in foci of adenomyosis. The reason for the increased tendency of focal bleeding in deep-seated adenomyotic foci is not understood [45–50]. In contrast, the ectopic endometrium at foci of endometriosis often undergoes circular changes, including degeneration, bleeding, and regeneration, which are similar to those seen in the functional layer of the endometrium. The different frequency of menstrual-type changes may be due to the relatively poor vascularity of the ectopic endometrium, which is a type of primary endometrium, compared to the endometriosis of the endometrium, which is rich in perspiration and is a type of functional layer of the endometrium. However, it appears to retain the ability to proliferate as a result it can develop and be responsible for the failure of amenorrhea or submenorrhea after endometrial destruction operations [45–50]. The secretory changes, which include the degradation of the layer in foci of adenomyosis, are observed mainly during pregnancy and treatment with exogenous progestogens and these changes are made through estrogen and progesterone receptors.

Progesterone effect in the non-pregnant uterus is observed in approximately 30–50% of foci of adenomyosis. During intrauterine pregnancy, 57% of the studies evaluated by Azziz found degeneration [39]. Other authors observed degeneration during pregnancy, only in deep foci, at a depth of at least two low-magnification optical fields, while degeneration was absent or insignificant in foci less than two low-magnification optical fields, the boundary of the basal layer of the endometrium-myometrium [45–52]. It is worth to be mentioned that adenomyosis can often be complicated by hyperplastic disorders up to atypia, while squamous cell carcinoma, mucosal metaplasia, and adenocarcinoma can occur in parallel with adenomyosis.

When the carcinoma is confined to an adenomyotic lesion, it should be considered "intravenous" as the prognosis is no worse than the carcinoma for which the patient underwent surgery. It is not possible to determine histologically whether the adenocarcinomas found in the supracervical uterus in foci of adenomyosis are the primary foci or the expansion of the endometrium into the foci of adenomyotic foci [45–52].

1.6 Clinical symptoms

Approximately 35% of adenomyosis cases are symptomatic [53–56]. In other cases, the most common symptoms are menorrhagia (50%), dysmenorrhea (30%) and uterine bleeding (20%). In some cases, discomfort may be an additional symptom. The frequency and severity of symptoms depend on the extent and depth of adenomyosis [53–56].

The exact cause of menorrhagia in patients with adenomyosis is not known. Menorrhagia may be due to poor contractility of the adenomyotic myometrium and compression of the endometrium by submucosal adenomas or leiomyomas. Mefenamic acid may reduce blood loss, suggesting that prostaglandin F2a (PGF2a) may play a role in the greater blood loss in women with adenomyosis [53–57]. Other factors may include anovulation, hyperplasia and, rarely, endometrial adenocarcinoma. Dysmenorrhea, finally, is due to the irritability of the uterus, which in turn is secondary to the increased amount of blood loss [58–60]. The symptoms associated with adenomyosis have not been analyzed by all researchers. For example, in

a study of 136 patients with histologically confirmed adenomyosis, the symptoms were varied, non-specific and, according to the researchers, associated with co-existing pathological conditions such as leiomyomas, endometriosis and polyps, rather than with adenomyosis [58–60]. In another prospective study, there were no differences in the incidence or severity of dysmenorrhea and pelvic pain between 28 women with adenomyosis and 157 controls [58–62]. A study of 23 women with myometrial adenomyosis reported no qualitative differences in spontaneous motility of isolated myometrial tissue during the menstrual cycle, compared with normal uterine fibroids [58–62]. The type of mobility was low-intensity and high-frequency automatic contractions during the reproductive phase, both of which increased during the secretory phase. Histamine-induced contractions of the myometrium were similar to all myometrial tissues tested [58–62].

Because the symptoms of adenomyosis are not specific, it is natural for the disease to be rarely diagnosed preoperatively. Most researchers report a correct preoperative diagnosis in less than 10% of cases [58–62]. However, due to the way the cases are selected, the incomplete pathological examination of the surgical specimens, and the limited number of well-designed studies, the true ability to diagnose adenomyosis is difficult to assess.

1.7 Diagnosis

The clinical diagnosis of adenomyosis is, at best, hypothetical (50%) and more often, it either does not occur (75%) [63–66] or the disease is overdiagnosed (35%) [63–66]. Menorrhagia and dysmenorrhea in a large woman, aged 40–50 years, raise the suspicion, but not the diagnosis, of adenomyosis. The uterus may be diffusely swollen, about the size of a 12-week pregnant uterus, and soft and tender to the touch. In addition, the presence of endometrial hyperplasia at the time of hysterectomy is the only variable directly related to adenomyosis [63–66].

Several researchers have used radiological methods to diagnose adenomyosis. In the largest hysterosalpingography study, Marshak and Eliasoph diagnosed adenomyosis in only 38 of 150 patients with proven adenomyosis [67]. However, they did not report either the total number of patients examined or the frequency of a false-positive diagnosis. The most common findings in hysterosalpingography are endometrial diversions and cellular invasions within the myometrium [67].

This test was considered inaccurate because myometrial adhesions attributed to adenomyosis resemble lymphatic or vascular infiltrations of the pigment. Intra-abdominal ultrasound is not useful in diagnosing adenomyosis. In the late 1970s, a group suggested that abnormal ultrasound areas of the myometrium, 5–7 mm in size, were an ultrasound finding characteristic of generalized adenomyosis [63–66].

This view was subsequently challenged by Siedler et al., who reported generalized uterine enlargement, normal uterine echogenicity, and retention of uterine shape in the majority of women with established adenomyosis. Subsequent studies have failed to clarify this issue [68].

Vaginal ultrasound has been used to diagnose adenomyosis since the early 1990s. Fedele estimated 43 women who would undergo hysterectomy for menorrhagia with preoperative transvaginal ultrasound. He described numerous small subsonic areas of the myometrium, with an abnormal ultrasound outline in 22 women [69].

The sensitivity of the method was estimated at 80% and specialization at 74%. Other researchers reported lower sensitivity, at 48 and 53% [70–80]. Other studies, with a larger number of women, are needed to address this issue [81–85].

Magnetic resonance imaging (MRI) has been applied to pelvic pathology and the initial results in women with adenomyosis are encouraging [75–84]. Mark and his colleagues predicted adenomyosis in eight of 20 women studied with T2 images. Ten

of the remaining 12 women were correctly diagnosed with adenomyosis free, while in two the diagnosis was uncertain [70].

The researchers described a typical, wide, low-density area surrounding the normal, high-density, endometrium in women with diffuse adenomyosis. Tiny foci of adenomyosis could not be diagnosed. T2 imaging has a significant advantage over shadowless imaging and that with T1 amplification. MRI has been used to differentially diagnose adenomyosis from leiomyomas [75–85].

Ninety-three patients were evaluated preoperatively and the results were related to surgical pathology. The 16 cases of adenomyosis were diagnosed preoperatively. The wider application of new technology needs, however, further evaluation. In addition, the cost can prevent MRI from becoming a widely used diagnostic test [75–85].

CA-125 is an antigen produced by the ovarian epithelial cells. It is secreted from these cells into the blood and is determined in a variety of gynecological diseases. Some researchers have used the determination of CA-125 levels to predict recurrences of non-mucosal ovarian cancers, while others have used it to diagnose recurrences of endometriosis. In the second case, successive determinations of CA-125 levels [75–85].

was required. In 1985, Takahashi and colleagues reported high preoperative CA-125 levels in six out of seven women with adenomyosis [70]. Although, CA-125 levels were elevated in these women, they were significantly lower than in patients with ovarian cancer. One month after hysterectomy, all women showed normal CA-125 levels. The same researchers, by immunohistochemical method, observed CA-125 production in the glandular epithelium of adenomyosis foci in eight hysterectomy specimens [75–88]. In another study, it was not possible to reproduce these results. In the report of 22 women, 11 of whom had adenomyosis, Halila and colleagues found normal preoperative CA-125 levels in all women with adenomyosis [71, 72]. These levels did not change significantly at one and five weeks after surgery. The cause of the different results in these studies was not clear, but it is hoped that future research will lead to some conclusions [71, 72].

Cysteine and leucine aminopeptidase levels have been used as possible markers of adenomyosis. Levels of these enzymes are elevated in various benign and malignant conditions of the uterus and ovaries [75–88].

However, no control studies have been performed to evaluate the clinical utility of these measurements. Although, adenomyosis can be diagnosed after a needle biopsy of the uterus, the sensitivity of this method is low and depends on the number of biopsies and the depth of penetration of the adenomyosis. This technique is of little or no importance in the diagnosis of minimal or moderate disease, but can provide histological confirmation in cases with extensive myometrial infiltration. If the biopsy confirms the diagnosis, women should be identified based on their history and tested for transvaginal ultrasound and MRI. These diagnostic methods can also help determine the location of the biopsy. However, myometrial biopsy, as a routine method, in women with pelvic pain should not be performed [75–88].

1.8 Treatment

Hysterectomy surgery remains the key approach in both the diagnosis and treatment of adenomyosis until a safer and more effective method of immediate biopsy is found. The only way to accurately diagnose adenomyosis is to remove the uterus, which also provides treatment for this condition, whereas prolactin, progesterone and growth hormone appear to accelerate the development of the disease [89–94].

RU 486, an anti-progesterone agent that inhibits the action of progesterone on its receptors in the uterus, suppresses the development of adenomyosis if administered for 30 days. Of course, they also require studies in humans [89–94]. There is

evidence that progesterone promotes the development of adenomyosis in humans as well as in muscles [89–94]. Danazol, an antigonadotropic derivative of testosterone 17α-ethinyl, has not been widely used in the treatment of adenomyosis [88].

From June 1993 to August 2000, Tamaoaka et al. treated adenomyosis women with endometrial glomeruli containing danatrol, and observed a marked reduction in dysmenorrhea and levels of CA-125 in women with endometrial hyperplasia. The histopathological findings of hyperplasia disappeared during the use of these endometrial glomeruli. The mechanism of the direct action of danatrol in endometrial hyperplasia has not been fully elucidated [89–94].

Hormone therapy with progestogens or gonadotropin-releasing hypothalamic hormone analogs (GnRH-α) could be as effective as in endometriosis [94–96]. However, an increase in uterine size and a recurrence of symptoms occur within six months of stopping treatment. Conservative surgical treatment may be helpful in some patients, although follow-up of women after such surgery is limited to three years [96–98].

The activity of one orally administered metalloproteinase inhibitor (ONO-4817) in the development of adenomyosis was recently tested experimentally by anterior pituitary gland transplantation into muscle. The results indicate that this drug could be activated the development of adenomyosis [96–98].

2. Uterine artery embolization

The uterine artery embolization (UAE) has been used successfully for refractory gynecologic problems in premenopausal women like: hemorrhage, pain, bulk symptoms, or a combination of them despite previously performed surgical procedures (myomectomy, adenomectomy) or medical treatment. The desire for minimally invasive alternatives for the management of symptomatic adenomyosis premenopausal women prompts interventional radiologists to propose UAE as an alternative treatment to surgical treatment of adenomyosis. According to various reports, the ability to improve menstrual disorders and symptoms of premenopausal women through UAE without the need for surgical procedures led to this method becoming famous. However, despite the positive comments of several reports exist no prospective randomized trials to determine the relative safety effectiveness of UAE compared either to surgical or medical options [78–84]. The cooperation between a gynecologist and interventional radiologist is obligatory to establish optimal clinical guidelines for premenopausal women care due to preinterventional consultation, procedural course and postprocedural follow up require gynecological and also radiological services.

2.1 UAE technical procedure

The target of the UAE is to administrate material polyvinyl alcohol (PVA). Microspheres or gelatin-coated tris-acryl polymer microspheres bilateral in uterine arteries to interrupt or reduce the blood supply at the level of the arterioles and to produce irretrievable ischemic damage, degeneration and shrinkage of adenomyosis focus without causing permanent damage to uterus. The target of UAE is an interruption or reduction of the blood supply of fibroids at the level of the arterioles after bilateral (from left and right) super-selective catheterization with microcatheters of the arteries that supply the fibroids and injection of acryl polymer embolospheres with a diameter of 500–900 μm for provocation of irretrievable ischemic damage to the fibroids. The aspects of the technical approach of UAE are summarized and described as follows: A single right femoral artery is typically catheterized after intravenous local analgesia and after that is performed pelvic arteriography to

define the vascular tree and identifiy both uterine arteries. All UAE procedures were carried out in the angio suite with a digital subtraction angiography (DSA) system. Except this is of great importance to exclude present vascular abnormalities. The goal of UAE is partial or complete occlusion of both uterine arteries branches which led to adenomyosis focus with polyvinyl alcohol (PVA). Microspheres or gelatin-coated tris-acryl polymer microspheres and after the embolization of the above-mentioned vessels may produce effective infraction of adenomyosis focus associated due to moderate or severe pain. It is very important to sparing of cervical and vaginal branches, vasoconstriction avoidance, catheter 4-F retraction in the internal iliac artery, after the microcatheter placement.

Caution for anatomic variances:

atypical origin of uterine arteries, ovarian/uterine tube arteries deriving from uterine arteries, multiple arteries branching instead of one artery, absence of uterine arteries, origin from ovarian arteries or round ligament arteries, avoidance of embolization of the ascending branches to the ovary and descending branches to the cervix and the vagina.

After the selective catheterization of the uterine artery visualization with contras, if major ovary branch is visualized micro catheter is moved superelectively inside the ovary branch and the embolization of the supply to the ovary is done first with microspheres or big embolospheres with a diameter 900 μm. Technical difficulties include severe cannulating of arteries due to anatomic variations, arterial spasm, recently use of gonadotropin releasing hormone agonist, uterine perfusion from collateral ovarian vasculature. During the procedure, analgesic treatment (paracetamol and morphine) is administered wherever it is necessary.

3. Our experience with UAE treatment in adenomyosis premenopausal women

Between April 2008 and 2021 sixty-four premenopausal women from our department Obstetrics and Gynecology, with symptomatic adenomyosis (diffuse adenomyosis), focal (adenomyoma) or coexisting with uterine myomas in fourty cases, ten cases and fourteen cases respectively underwent uterine artery embolization (UAE) in cooperation with Interventional Radiology department of Democritus University of Thrace, Greece. All procedures were performed by the institutional ethical standards and with the 1964 Helsinki Declaration.

Informed consent was obtained from all individual participants included in the study. All study participants with adenomyosis with or without concomitant fibroids were assessed for treatment by an experienced gynecologist.

With a medical history, the main symptoms were divided into the following categories: menstrual bleeding, pelvic pain (rated on a VAS score from 0 to 10, with 0 representing no pain and 10 unbearable pain), urinary discomfort, bleeding pain, massive symptoms, combination despite previous treatment, and health-related quality of life effects (restrictions on daily activities, energy/mood, self-awareness, and sexual function). Each participant then underwent a gynecological clinical examination, also transvaginal ultrasound followed by an MRI study. All imaging findings [US/MRI transvaginal ultrasound in either a Tesla 1 scanner (GE Healthcare) or a 1.5 Tesla magnet (Philips Multiva)] were then evaluated by an experienced gynecologist and invasive radiologist for possible treatment in the UAE. We present from our study participants Figures from a case with mixed adenomyosis and myoma uteri (**Figures 1-6**). Additional laboratory tests were performed that included platelet count, clotting time, and renal function markers (creatinine and glomerular filtration rate). All the methods and procedures followed in the present study obey the basic ethical rules. The study was

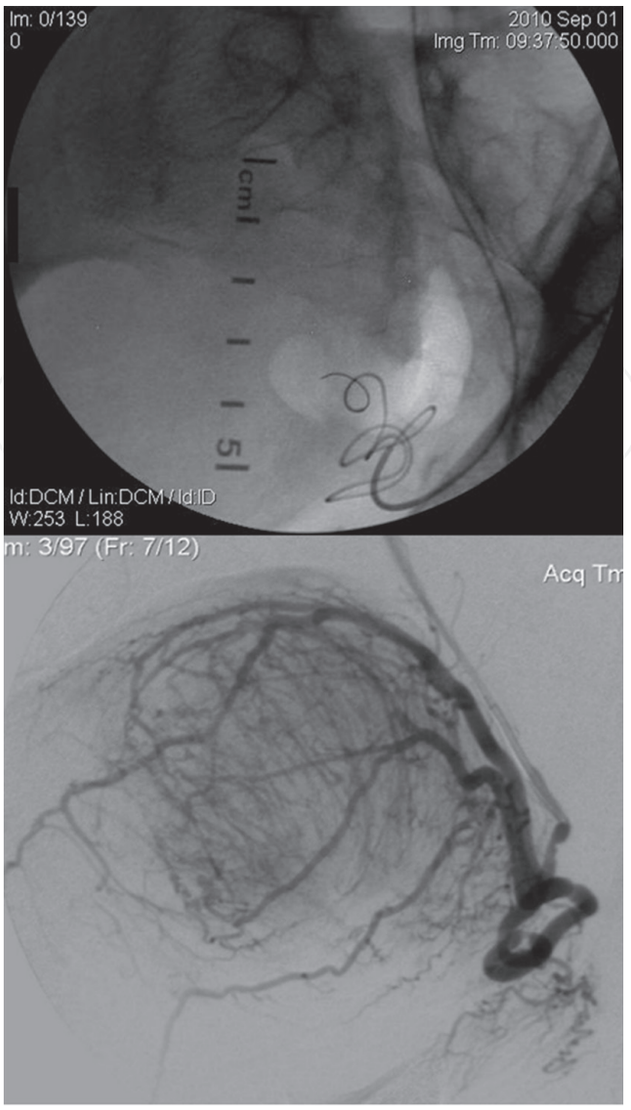

Figure 1.
Uterus myoma straight vessels.

conducted under the Helsinki Declaration. After detailed information of the participants regarding treatment options by the gynecologist and the invasive radiologist, written consent from every single one of the participants was obtained. Study participants were admitted to the University Obstetrics and Gynecology Clinic one day before the uterine artery embolization and underwent laboratory tests. On the procedure day they were receiving intravenous chemoprophylaxis and in particular iv Augmentin 600 mg and iv Metronidazole 1 g, while four hours before the UAE a urinary catheter was placed. Following the procedure, all participants received additional analgesic treatment every 4 h (tramadol 100 mg) and were monitored at the Department of University Obstetrics and Gynecology.

The clinical results of the study were based on evaluations concerning the overall satisfaction of the patients, the relief of clinical symptoms, the need for reoperation and hysterectomy and the amenorrhea rates during the follow-up period, which varied from 1 to 12 months.

3.1 Exclusion criteria

Included were postmenopausal women, patients with severe co-morbidities, patients who wished to maintain their fertility, patients with a known allergy to the contrast agent used during the procedure, and patients with suspected malignancy.

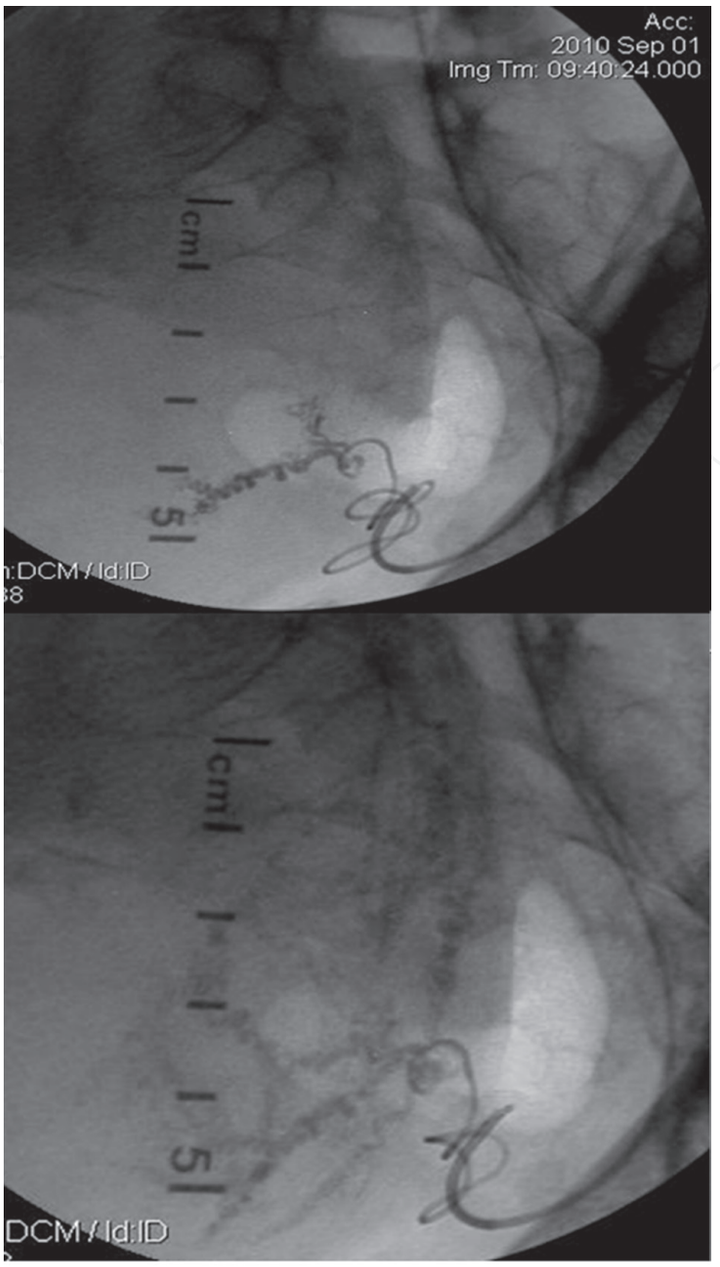

Figure 2.
Adenomyosis uteri spiral vessels.

There was no planned pregnancy or pelvic inflammation in the participants, while patients with only symptoms of back pain, asymptomatic, fibroid pendulum and rapidly improved size were excluded from the present study.

3.2 Study participants

A total of 64 patients met the inclusion criteria, with a mean admission age of 51 years (36–53). 40 patients (62.5%) were diagnosed with pure adenomyosis, 10 patients (15.62%) with focal adenomyosis (adenomyoma) and 14 patients (21.87%) with adenomyosis and fibroids. 50 participants (78%) had a history of pregnancy and childbirth in the past.

Reported symptoms included: dysmenorrhea (98%) with a mean VAS score of 8.8 (range 6–10), menorrhagia with menstrual clots (88%), menorrhagia without menstrual clots (53%) and urinary problems (12%). In terms of quality of life data, 76.5% of women complained of limited daily activities and low energy due to heavy menstrual bleeding, while 73.5% had problems with their sex life.

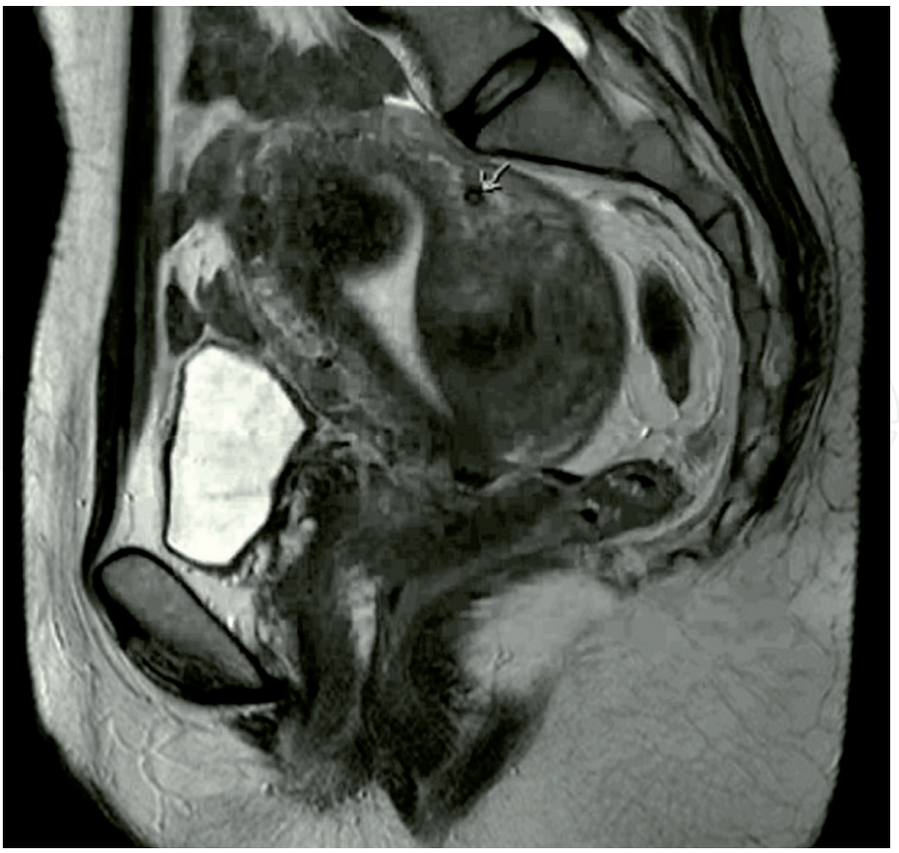

Figure 3.
Mixed type adenomyosis, myomas predominate, pressing and repelling the endometrium. MRI section, T2-WI, Sagital. Notice the increase in the width of the myometrial transition zone and hemosiderin granule (arrow) in the enlarged transition zone.

3.3 Results

According to our results, we confirm the following data:

Successful embolization (100%) was observed in all participants. On average, patients spent two days in the hospital, one day before the procedure and one on the day of the intervention. Elimination of clinical symptoms and reduction in pelvic pain intensity, assessed using VAS, was observed in 62 participants (96.87%). Pain in these cases decreased by an average of 7.5 points (from 8.2 to 1.0 points) during the follow-up period (from 1 to 12 months, average 3 months). Severe pain immediately after embolization and for approximately 24 h was observed in 8 cases with diffuse adenomyosis, 4 cases with adenomyoma and 2 cases with coexisting adenomyosis, in which analgesics and non-steroidal anti-inflammatory drugs were administered. In the majority of participants in our study, there were no significant complications associated with the procedure. However, in 4 participants (6.2%) recurrence of pain was observed within one to 2 months after embolism. In these cases, fractional dissolution is required, because submucosal fibroids coexist and adenomyosis diffuses. A postpartum neonatal ward of focal adenomyosis, sepsis, and surgical resection of necrotic sections was established, subject to the uterus. In no case was either reoperation or hysterectomy required. Restoration of normal menstruation was immediately observed in the subgroup of participants under 45 years of age. The other subgroup, which included participants over the age of 45, had normal menstruation. Only in 93% of cases immediately and only in 4 participants reported experience of the absence of menstruation for at least 3 months after embolization, resulting in the appearance of the period later after three months than in the other participants. In participants of the older participants over 45 years

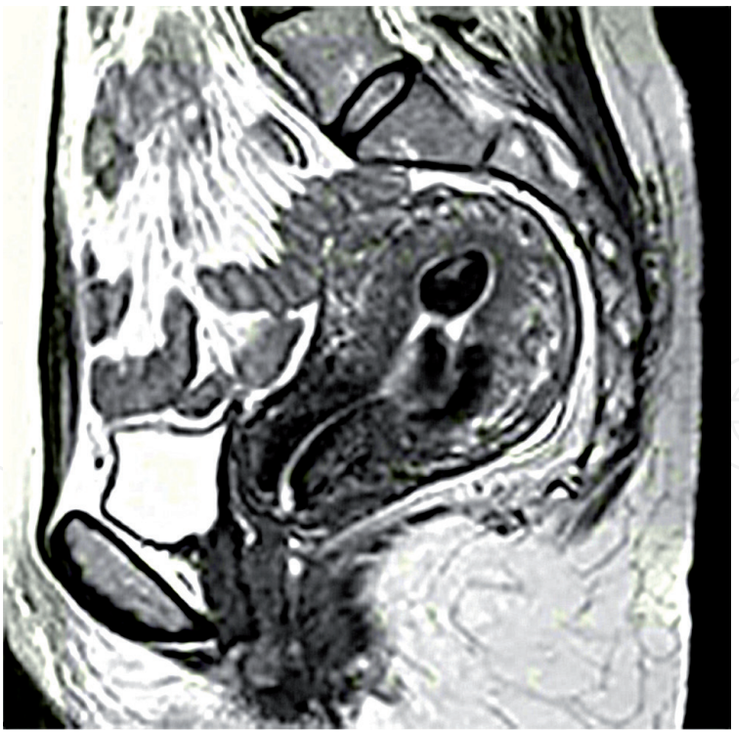

Figure 4.
MRI section, T2-WI, Sagital of the patient, six months after bilateral embolization. The myomas have completely degenerated and shrunk, however they continue to repel the endometrium to a lesser degree. The myometrial band anatomy has been restored to normal. The examination was performed with sections T2-WI, D-WI and T1-WI, simple and with spectral suppression of the magnetic fat signal, before and after intravenous administration of paramagnetic substance—situation after UAE 6 months ago. Degeneration, complete elimination of vasculitis and very significant further shrinkage of the two submucosal myomas, degeneration, ischemia and mild further shrinkage of the subarachnoid myoma of the anterior myometrium are observed, while the muscles of the fibroids are completely indistinguishable. The (normal) endometrium is slightly repelled by the two submucosal myomas. In the present examination, the uterus, which has been reduced in size, is presented with normal belt anatomy. Normal imaging of the cervix—a little free peritoneal liquid is shown in the Douglas pouch—the ovaries are normal—no pathological lymph nodes are not detected.

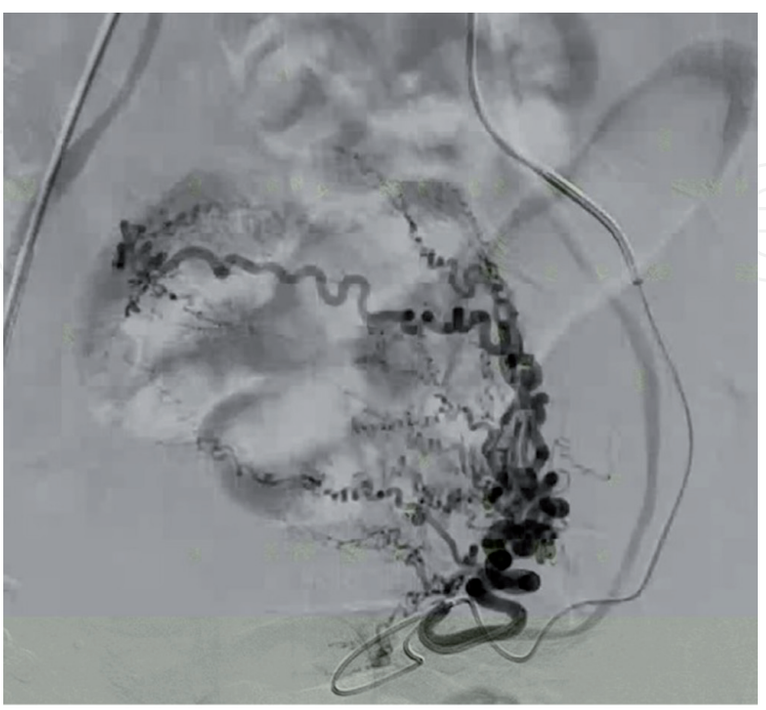

Figure 5.
Hyperelective catheterization and imaging before embolization of the left uterine artery, using a microcatheter. Observe the spiral vessels of adenomyosis and the straight lines of the myomas.

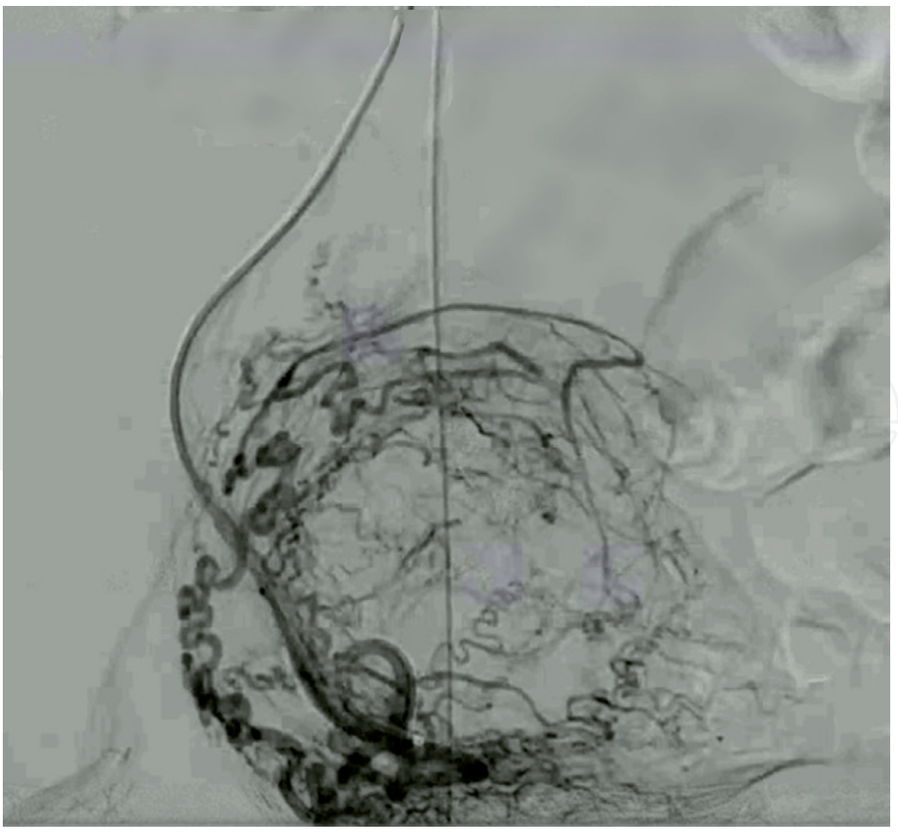

Figure 6.
Hyperelective catheterization and imaging before embolization of the right uterine artery, using a micro-catheter.

with a delayed onset of menstruation, low levels of AMH were established depending on biological age. Based on the findings of the MRI, partial or complete restoration of the normal zone anatomy in the uterus was confirmed after 6 months. All participants reported a decrease in menstrual bleeding and consequently improvement of everyday life quality. In one woman aged 49 years old, the decrease was not satisfactory and she underwent two months of analgesics therapy and after that the clinical symptoms were successfully improved. In our participants, the avoidance of hysterectomy was achieved in 100% of the women. All participants reported to be very or fairly satisfied with the results and would recommend this treatment to colleagues and friends.

4. Discussion

Adenomyosis is reasonable, although it has not been proven, that matrices with adenomyosis are deficient in activated T-cells, with the result that the basal endometrium in adenomyosis has an advantage in terms of growth potential over non-adenomyotic and lymphoid-rich basal formations. The adenomyosis led to reducing the junctional zone thickness whereas the latter results in the reduction of uterine volume. It remains a major problem that the diagnosis is based on its variable presentation and common coexistence of other gynecologic disorders like fibroids or endometriosis. Growth of adenomyosis focus proved due to contrast-enhanced MRI and TVUS are recommended currently as the most accurate imaging techniques for the diagnosis of the disease. The classical surgical procedure, hysterectomy, is recommended as the only definite treatment modus, while the other treatment alternatives medical and UAE are widely implemented and exist controversially reports [94–98].

Both treatments are reported to be successful, especially in the short term, but there are some long-term reports of UAE adenomyosis treatment being poor in success rate and reaching almost 50% of patients receiving treatment without reporting clinical improvement. Regarding the previously published reports, a recurrence rate of 38% was reported, satisfactory life results were observed in 76% of the participants. However, the question remains unanswered whether such an abnormality is necessarily associated with acquired "morbidity" of the myometrium or whether it is an independent condition for the development of adenomyosis. The exact cause of hyperplasia-hypertrophy of the myometrium, located around the deep foci of the endometrium, is not known [94–98].

Myometrial hyperplasia-hypertrophy may indicate either an attempt to control endometrial penetration or simply represent bundles of smooth muscle fibers displaced by the expanding endometrium. After examination, by immunohistochemical technique, it was found that the myometrium, which surrounds the ectopic endometrium either diffuse (adenomyosis) or focal (adenomyoma), does not show abnormalities. Smooth muscle cells in adenomyotic foci, normal myometrium and leiomyomas, whether or not coexisting with adenomyosis, are rich in actin and desmin [94–98]. Several experimental "models" have been reported to study the pathogenesis of adenomyosis. In one of them, endometrial grafts of the anterior pituitary gland in mice led to the development of adenomyosis [98–100]. Prolactin may amplify this, as the uterine horn that did not contain isografts showed relatively less development of adenomyosis. In this experimental model ovarian resection was prevented, while benzoic estradiol favored the development of adenomyosis.

In another mouse model, which received high doses of diethylstilbestrol (DES) during fetal life, adenomyosis developed. These genera of mice appear to be prone to developing adenomyosis when there are high concentrations of prolactin, estrogen and progestogens. More recently, other researchers have induced adenomyosis in uncastrated rats with hyperprolactinaemia [98–104].

The researchers argued that high concentrations of prolactin cause degeneration of the myometrium, with the concomitant presence of ovarian steroids, which leads to its weakening, resulting in the invasion of the basal layer of the endometrium. Also of great interest were the observations of Mori and Nagasawa in mice, in which the penetration of stromal fibroblasts along the branches of the myometrial blood vessels preceded the invasion of the endometrial glands [105].

In another study, Sakamoto et al., caused severe adenomyosis of the uterus in mice by placing ectopic anterior pituitary lobe isografts [106]. DNA synthesis-related activities and related enzymes, such as thymidyl synthetase and thymidine kinase, were significantly increased in adenomyosis matrices, compared with controls in the control group. In the same experimental model, it was found that finding low molecular weight metalloproteinases plays a role in the development of adenomyosis, at the level of gene transcription, activation and repression [99–108]. Specific experimental observations suggest that hereditary factors may be involved in the pathogenesis of adenomyosis. For example, the matrices of recombinant SMXA mice automatically develop adenomyosis-like histological changes and contain tenascin around the adenomyotic glands [100–108]. These observations, together with the biological properties of tenascin, reinforce the view of the endometrial origin of adenomyosis and the idea of endometrial penetration into the myometrium, which is genetically predisposed.

Also, compared to SMXA mice, the matrices of F1 mice, a genus found between SMXA and NJL, contain even more obvious spontaneous changes, resembling human adenomyosis. It should be noted, however, that it has not yet been determined whether heredity is an important factor in the development of adenomyosis in humans [100–108]. The early development of adenomyosis from remnants

of Müller's ducts, in positions outside the uterus, is enhanced by the finding of adenomyosis in the rectal septum [100–108]. In this anatomical position can be found endometrial glands and layers, which are associated with hypertrophy of the adjacent smooth muscle fibers and form adenomyotic nodules [100–108]. Although, these nodules can develop as a result of penetration of the peritoneal endometriosis of their origin from remnants of Müller's resources. Thus, according to Nisolle and Donnez, in most cases, adenomyotic nodules are located deep in the septum and in some cases in the muscular layer of the rectum, away from the pelvic peritoneum [106–108]. The co-expression of vimentin and cytokeratin in the endometrium, when it is located in the endometrial cavity and when it is located in adenomyotic foci, is a typical feature of tissue, derived from Müller's ducts. Morphologically and in terms of receptor content, adenomyosis of the atrial septum is similar to that of the myometrium, including poor or no response to the post-ovulatory effect of progesterone. Despite the high doses of progestogens in women with rectal adenomyosis to induce secretory differentiation, hormone therapy has poor results. The definitive treatment of the rectal lesions with surgery also suggests the existence of a metaplastic process from the beginning, from remnants of Müller's ducts in this position, despite the implantation and penetration by peritoneal endometriosis [109–119].

Therefore, as the pathogenetic mechanisms of adenomyosis remain unclear, more studies are needed to reveal the pathophysiology of the disease. In the present study, all patients presented improvement in menorrhagia and had less blood loss during menstruation, while the effectiveness of the method appeared to be higher than that of other conservative surgeries such as intra-myometrial resection/excision and adenoectomy and laparoscopic myometrial electrocoagulation [119–125]. Radical surgery such as hysterectomy was eventually avoided in all participants, in 100% of the 64 patients. We did not observe the occurrence of permanent menopause, except in 0.6% of the participants, while transient amenorrhea within the first 3 months, occurred in the subgroup over the age of 45 years [119–125]. Premature menopause induction and subclinical reduction of ovarian functional reserve after the UAE is a known complication of this procedure, however, we have not observed any cases [119–125]. We know that our study has limitations and that the small sample size precludes a more detailed statistical analysis. Also, when adenomyosis coexists with uterine fibroids, it is very difficult to determine if the symptoms are caused by adenomyosis or the other. The incidence of pure adenomyosis is relatively low and due to a rare condition, individuals with co-existing fibroids were included [119–125].

5. Conclusions

In conclusion, despite the small number of participants, our preliminary study showed promising results with a very high rate of satisfied patients confirming that UAE might be a safe and effective method of treatment for premenopausal women with symptomatic adenomyosis in different if occurs with or without fibroids. It is a non-amputating treatment, alternative to hysterectomy UAE, for the treatment of symptomatic adenomyosis, when conservative treatment fails associated with few complications and allowed an option for the new session for recurrent disease.

Conflict of interest

None.

Notes/thanks/other declarations

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References

[1] Matalliotakis IM, Kourtis AI, Panidis DK. Adenomyosis. Obstetrics and Gynecology Clinics of North America. 2003;**30**(1):63-82, viii

[2] Siegler AM, Camilien L. Adenomyosis. The Journal of Reproductive Medicine. 1994;**39**(11):841-853

[3] Kissler S, Gaetje R, Siebzehnruebl E, Kaufmann M. New aspects in diagnosis and therapy of endometriosis. Zentralblatt für Gynäkologie. 2004; **126**(5):299-302 Review

[4] Ben Hamouda S, Ouerdiane N, Ben Zina H, et al. Adenomyosis at hysterectomy. La Tunisie Médicale. 2007;**85**(7):559-562

[5] Levgur MJ. Diagnosis of adenomyosis: A review. Reproductive Medicine. 2007;**52**(3):177-193

[6] Kissler S, Zangos S, Kohl J, et al. Duration of dysmenorrhoea and extent of adenomyosis visualised by magnetic resonance imaging. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2008;**137**(2): 204-209

[7] Adamyan L, Aznaurova Y, Stepanian A, et al. Gene expression signature of endometrial samples from women with and without endometriosis. Journal of Minimally Invasive Gynecology. 2021;**S1553-4650**(21): 00170-00179

[8] Bernardi M, Lazzeri L, Perelli F, et al. Dysmenorrhea and related disorders. F1000Research. 2017;**6**:1645. DOI: 10.12688/f1000research.11682.1. eCollection 2017

[9] Yang TWS, Ahn JMLJY. The molecular basis of adenomyosis development. Journal of Embryo Transfer. 2018;**33**(1):49-54. DOI: 10.12750/JET.2018.33.1.49

[10] Kay N, Huang C-Y, Shiu L-Y, et al. Neutralization improves pregnancy outcomes by restoring endometrial receptivity in mice with adenomyosis. Reproductive Sciences. 2021;**28**(3): 877-887

[11] Benagiano G, Brosens I. History of adenomyosis. Best Practice & Research: Clinical Obstetrics & Gynaecology. 2006;**20**(4):449-463

[12] Benagiano G, Brosens I, Lippi D. The history of endometriosis. Gynecologic and Obstetric Investigation. 2014; **78**(1):1-9

[13] Tamai K, Koyama T, Umeoka S, et al. Spectrum of MR features in adenomyosis. Best Practice & Research. Clinical Obstetrics & Gynaecology. 2006;**20**(4):583-602

[14] Marcus CC. Relationship of adenomyosis uteri to endometrial hyperplasia and endometrial carcinoma. American Journal of Obstetrics and Gynecology. 1961;**82**:408-416

[15] Bird CC, McElin TW, Manalo-Estrella P. The elusive adenomyosis of the uterus—Revisited. American Journal of Obstetrics & Gynecology. 1972;**112**(5):583-593

[16] Hudelist G, Keckstein J, Wright JT. The migrating adenomyoma: Past views on the etiology of adenomyosis and endometriosis. Fertility and Sterility. 2009;**92**(5):1536-1543

[17] Benagiano G, Brosens I, Habiba M. Structural and molecular features of the endomyometrium in endometriosis and adenomyosis. Human Reproduction Update. 2014;**20**(3):386-402

[18] Owolabi TO, Strickler RC. Adenomyosis: A neglected diagnosis. Obstetrics and Gynecology. 1977;**50**(4): 424-427

[19] Upson K, Missmer SA. Epidemiology of adenomyosis. Seminars in Reproductive Medicine. 2020;**38**(2-03):89-107

[20] Yu O, Schulze-Rath R, Grafton J, et al. Adenomyosis incidence, prevalence and treatment: United States population-based study 2006-2015. American Journal of Obstetrics and Gynecology. 2020;**223**(1):94

[21] Vercellini P, Viganò P, Somigliana E, et al. Adenomyosis: Epidemiological factors. Best Practice & Research. Clinical Obstetrics & Gynaecology. 2006;**20**(4):465-477. Review

[22] Upson K, Missmer SA. Epidemiology of adenomyosis. Seminars in Reproductive Medicine. 2020; **38**(2-03):89-107

[23] Naphatthalung W, Cheewadhanaraks S. Prevalence of endometriosis among patients with adenomyosis and/or myoma uteri scheduled for a hysterectomy. Journal of the Medical Association of Thailand. 2012;**95**(9):1136-1140

[24] Upson K, Missmer SA. Epidemiology of adenomyosis. Seminars in Reproductive Medicine. 2020;**38**(2-03):89-107

[25] Milingos S, Protopapas A, Drakakis P, et al. Laparoscopic management of patients with endometriosis and chronic pelvic pain. Annals of the New York Academy of Sciences. 2003;**997**:269-273

[26] Vercellini P, Trespidi L, De Giorgi O, et al. Endometriosis and pelvic pain: Relation to disease stage and localization. Fertility and Sterility. 1996;**65**(2):299-304

[27] Ridley JH. The validity of Sampson's theory of endometriosis. American Journal of Obstetrics and Gynecology. 1961;**82**:777-782

[28] Vollmer G, Siegal GP, Chiquet-Ehrismann R, Lightner VA, Arnholdt H, Knuppen R. Tenascin expression in the human endometrium and in endometrial adenocarcinomas. Laboratory Investigation. 1990;**62**(6): 725-730

[29] Matsuda M, Sasabe H, Adachi Y, et al. Increased invasion activity of endometrial stromal cells and elevated expression of matrix metalloproteinase messenger RNA in the uterine tissues of mice with experimentally induced adenomyosis. American Journal of Obstetrics and Gynecology. 2001;**185**(6):1374-1380

[30] Goumenou AG, Arvanitis DA, Spandidos DA. Loss of heterozygosity in adenomyosis on hMSH2, hMLH1, p16Ink4 and GALT loci. International Journal of Molecular Medicine. 2000; **6**(6):667-671

[31] Bulun SE, Yildiz S, Adli M, et al. Adenomyosis pathogenesis: Insights from next-generation sequencing. Human Reproduction. 2021;**27**(6):1086-1097. DOI: 10.1093/humupd/dmab017

[32] Lacheta J. Uterine adenomyosis: Pathogenesis, diagnostics, symptomatology and treatment. Ceská Gynekologie. 2019;**84**(3):240-246. Review

[33] Vannuccini S, Tosti C, Carmona F, et al. Pathogenesis of adenomyosis: An update on molecular mechanisms. Reproductive Biomedicine Online. 2017;**35**(5):592-601

[34] Antero MF, Ayhan A, Segars J, Shih IM. Pathology and pathogenesis of adenomyosis. Seminars in Reproductive Medicine. 2020;**38**(2-03):108-118

[35] Guo SW. The pathogenesis of adenomyosis vis-a-vis endometriosis. Journal of Clinical Medicine. 2020; **9**(2):485

[36] Antero MF, Ayhan A, Segars J, Shih IM. Pathology and pathogenesis of adenomyosis. Seminars in Reproductive Medicine. 2020;**38**(2-03):108-118

[37] Zhai J, Vannuccini S, Petraglia F. et al, Adenomyosis: Mechanisms and pathogenesis. Seminars in Reproductive Medicine. 2020;**38**(2-03):129-143

[38] García-Solares J, Donnez J, Donnez O, et al. Pathogenesis of uterine adenomyosis: Invagination or metaplasia? Fertility and Sterility. 2018;**109**(3):371-379

[39] Langlois PL. The size of the normal uterus. The Journal of Reproductive Medicine. 1970;**4**(6):220-228

[40] Mark AS, Hricak H, Heinrichs LW, et al. Adenomyosis and leiomyoma: Differential diagnosis with MR imaging. Radiology. 1987;**163**(2):527-529

[41] Sandberg EC, Cohn F. Adenomyosis in the gravid uterus at term. American Journal of Obstetrics & Gynecology. 1962;**84**:1457-1465

[42] Azziz R. Adenomyosis in pregnancy. A review. Journal of Reproductive Medicine. 1986;**31**(4):224-227

[43] Parazzini F, Mais V, Cipriani S, et al. Determinants of adenomyosis in women who underwent hysterectomy for benign gynecological conditions: Results from a prospective multicentric study in Italy. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2009;**143**(2):103-106

[44] Song Y, Fazleabas AT. Endometrial organoids: A rising star for research on endometrial development and associated diseases. Reproductive Sciences. 2021;**28**(6):1626-1636. Review

[45] Zhu J, Mayr D, Kuhn C, Mahner S, et al. Prostaglandin E2 receptor EP1 in healthy and diseased human endometrium. Histochemistry and Cell Biology. 2018;**149**(2):153-160

[46] Ben Hamouda S, Ouerdiane N, Ben Zina H. et al, Adenomyosis at hysterectomy. La Tunisie Médicale. 2007;**85**(7):559-562

[47] Bergeron C, Amant F, Ferenczy A. Pathology and physiopathology of adenomyosis. Best Practice & Research. Clinical Obstetrics & Gynaecology. 2006;**20**(4):511-521. Review

[48] McLucas B. Diagnosis, imaging and anatomical classification of uterine fibroids. Best Practice & Research. Clinical Obstetrics & Gynaecology. 2008;**22**(4):627-642. Review

[49] Kishi Y, Shimada K, Fujii T, et al. Phenotypic characterization of adenomyosis occurring at the inner and outer myometrium. PLoS One. 2017;**12**(12):e0189522

[50] Azziz R. Adenomyosis: Current perspectives. Obstetrics and Gynecology Clinics of North America. 1989;**16**(1): 221-235. Review

[51] Graham KJ, Hulst FA, Vogelnest L, et al. Uterine adenomyosis in an orang-utan (Pongo abelii/pygmaeus). Australian Veterinary Journal. 2009;**87**(1):66-69. Review

[52] Basak S, Saha A. Adenomyosis: Still largely under-diagnosed. The Obstetrician and Gynaecologist. 2009;**29**(6):533-535

[53] Chapron C, Vannuccini S, Pistofidis G, Petraglia F. Diagnosing adenomyosis: An integrated clinical and imaging approach. Human Reproduction Update. 2020;**26**(3): 392-411

[54] Struble J, Reid S, Bedaiwy MA. Adenomyosis: A clinical review of a challenging gynecologic condition. Journal of Minimally Invasive Gynecology. 2016;**23**(2):164-185

[55] Munro MG. Classification and reporting systems for adenomyosis. Journal of Minimally Invasive Gynecology. 2020;**27**(2):296-308

[56] Vannuccini S, Petraglia F. Recent advances in understanding and

managing adenomyosis. F1000Research. 2019;**8**:F1000. Faculty Rev-283

[57] Panganamamula UR, Harmanli OH, Isik-Akbay EF, et al. Is prior uterine surgery a risk factor for adenomyosis? Obstetrics and Gynecology. 2004;**104**(5 Pt 1):1034-1038

[58] Kdous M, Ferchiou M, Zhioua F. Uterine adenomyosis, clinical and therapeutic study: About 87 cases. The Pan African Medical Journal. 2015;**22**:73

[59] Kilkku P, Erkkola R, Grönroos M. Non-specificity of symptoms related to adenomyosis. A prospective comparative survey. Acta Obstetricia et Gynecologica Scandinavica. 1984;**63**(3):229-231

[60] Peric H, Fraser IS. The symptomatology of adenomyosis. Best Practice & Research: Clinical Obstetrics & Gynaecology. 2006;**20**(4):547-555. DOI: 10.1016/j.bpobgyn.2006.01.006. Epub 2006 Mar 2

[61] Levgur M, Abadi MA, Tucker A. Adenomyosis: Symptoms, histology, and pregnancy terminations. Obstetrics and Gynecology. 2000;**95**(5):688-691

[62] Morita M, Asakawa Y, Kubo H, et al. Laparoscopic excision of myometrial adenomyomas in patients with adenomyosis uteri and main symptoms of severe dysmenorrhea and hypermenorrhea. The Journal of the American Association of Gynecologic Laparoscopists. 2004;**11**(1):86-89

[63] Parrott E, Butterworth M, Greaves P, et al. Adenomyosis—A result of disordered stromal differentiation. American Journal of Pathology. 2001; **159**(2):623-630

[64] Nisolle M, Donnez J. Peritoneal endometriosis, ovarian endometriosis, and adenomyotic nodules of the rectovaginal septum are three different entities. Fertility and Sterility. 1997;**68**(4): 585-596

[65] Wilde S, Scott-Barrett S. Radiological appearances of uterine fibroids. Indian Journal of Radiology and Imaging. 2009;**19**(3):222-231

[66] Takeuchi M, Matsuzaki K. Adenomyosis: Usual and unusual imaging manifestations, pitfalls, and problem-solving MR imaging techniques. Radiographics. 2011;**31**(1): 99-115. Review

[67] Marshak RH. Eliasoph The roentgen findings in adenomyosis. Journal of Radiology. 1955;**64**(6):846-851

[68] Siedler D, Laing FC, Wing VW, et al. Uterine adenomyosis. A difficult sonographic diagnosis. Journal of Ultrasound in Medicine. 1987;**6**(7): 345-349

[69] Mark AS, Hricak H, Heinrichs LW, Hendrickson MR, Winkler ML, Bachica JA, et al. Adenomyosis and leiomyoma: Differential diagnosis with MR imaging. Radiology. 1987;**163**(2): 527-529

[70] Takahashi K, Kijima S, Yoshino K, et al. Differential diagnosis between leiomyomata uteri and adenomyosis using CA 125 as a new tumor marker of ovarian carcinoma. Nihon Sanka Fujinka Gakkai Zasshi. 1985;**37**(4): 591-595

[71] Babacan A, Kizilaslan C, Gun I, Muhcu M, Mungen E, Atay V. CA 125 and other tumor markers in uterine leiomyomas and their association with lesion characteristics. International Journal of Clinical and Experimental Medicine. 2014;**7**(4):1078-1083

[72] Halila H, Suikkari AM, Seppälä M. The effect of hysterectomy on serum CA 125 levels in patients with adenomyosis and uterine fibroids. Human Reproduction. 1987;**2**(3):265-266

[73] Zhou Y, Wu B, Li H. The value of serum CA125 assays in the diagnosis of

uterine adenomyosis. Zhonghua Fu Chan Ke Za Zhi. 1996;**31**(10):590-593

[74] Masahashi T, Matsuzawa K, Ohsawa M, Narita O, Asai T, Ishihara M. Serum CA 125 levels in patients with endometriosis: Changes in CA 125 levels during menstruation. Obstetrics and Gynecology. 1988;**72**(3 Pt 1):328-331

[75] Bergeron C, Amant F, Ferenczy A. Pathology and physiopathology of adenomyosis. Best Practice & Research. Clinical Obstetrics & Gynaecology. 2006;**20**(4):511-521. Epub 2006 Mar 24 Review

[76] Babacan A, Kizilaslan C, Gun I, Muhcu M, Mungen E, Atay V. CA 125 and other tumor markers in uterine leiomyomas and their association with lesion characteristics. International Journal of Clinical and Experimental Medicine. 2014;**7**(4):1078-1083

[77] Levy G, Hill MJ, Plowden TC, Catherino WH, Armstrong AY. Biomarkers in uterine leiomyoma. Fertility and Sterility. 2013;**99**(4): 1146-1152

[78] Ayas S, Bayraktar M, Gürbüz A, et al. Uterine junctional zone thickness, cervical length and bioelectrical impedance analysis of body composition in women with endometriosis. Balkan Medical Journal. 2012;**29**(4):410-413

[79] Yang CC, Tseng JY, Wang PH. Uterus didelphys with cervical agenesis associated with adenomyosis, a leiomyoma and ovarian endometriosis. A case report. Journal o Reproductive Medicine. 2002;**47**(11):936-938

[80] Woodruff JD, Erozan YS, Genadry R. Adenocarcinoma arising in adenomyosis detected by atypical cytology. Obstetrics and Gynecology. 1986;**67**(1):145-148

[81] Kay S, Frable WJ, Goplerud DR. Endometrial carcinoma arising in a large polypoid adenomyoma of the uterus. International Journal of Gynecological Pathology. 1988;**7**(4):391-398

[82] Yen CF, Huang SJ, Liao SK, et al. Molecular characteristics of the endometrium in uterine adenomyosis and its biochemical microenvironment. Reproductive Sciences. 2017;**24**(10): 1346-1361

[83] Özkan ZS, Kumbak B, Cilgin H, Simsek M, Turk BA. Coexistence of adenomyosis in women operated for benign gynecological diseases. Gynecological Endocrinology. 2012;**28**(3): 212-215

[84] Donnez J, Nisolle M, Casanas-Roux F, Bassil S, Anaf V. Rectovaginal septum, endometriosis or adenomyosis: Laparoscopic management in a series of 231 patients. Human Reproduction. 1995;**10**(3): 630-635

[85] Leyendecker G, Kunz G, Kissler S, Wildt L. Adenomyosis and reproduction. Best Practice & Research: Clinical Obstetrics & Gynaecology. 2006;**20**(4):523-546

[86] Chen M, Luo L, Wang Q, et al. Impact of gonadotropin-releasing hormone agonist pre-treatment on the cumulative live birth rate in infertile women with adenomyosis treated with IVF/ICSI: A retrospective Cohort study. Frontiers in Endocrinology (Lausanne). 2020;**11**:318

[87] Leyendecker G, Kunz G, Wildt L. Adenomyosis and reproduction. Best Practice & Research: Clinical Obstetrics & Gynaecology. 2006;**20**(4): 523-546

[88] Katsikogiannis N, Tsaroucha A, Simopoulos C. Rectal endometriosis causing colonic obstruction and concurrent endometriosis of the appendix: A case report. Journal of Medical Case Reports. 2011;**5**:320

[89] Li JJ, Chung JPW, Duan H. The investigation and management of adenomyosis in women who wish to improve or preserve fertility. BioMed Research International. 2018;**2018**: 6832685

[90] Tamura H, Kishi H, Kitade M, et al. Clinical outcomes of infertility treatment for women with adenomyosis in Japan. Reproductive Medicine and Biology. 2017;**16**(3):276-282

[91] Di Spiezio SA, Calagna G, Santangelo F, et al. The role of hysteroscopy in the diagnosis and treatment of adenomyosis. BioMed Research International. 2017;**2017**: 2518396

[92] Leyendecker G, Bilgicyildirim A, Inacker M, et al. Adenomyosis and endometriosis. Re-visiting their association and further insights into the mechanisms of auto-traumatisation. An MRI study. Archives of Gynecology and Obstetrics. 2015;**291**(4):917-932

[93] Ferrari F, Arrigoni F, Miccoli A, et al. Effectiveness of Magnetic Resonance-guided Focused Ultrasound Surgery (MRgFUS) in the uterine adenomyosis treatment: Technical approach and MRI evaluation. La Radiologia Medica. 2016;**121**(2):153-161

[94] Gao Y, Shan S, Zhao X, et al. Clinical efficacy of adenomyomectomy using "H" type incision combined with Mirena in the treatment of adenomyosis. Medicine (Baltimore). 2019;**98**(11): e14579

[95] Kishi Y, Yabuta M. The benefit of adenomyomectomy on fertility outcomes in women with rectovaginal endometriosis with coexisting adenomyosis. Gynecology and Minimally Invasive Therapy. 2017;**6**(1):20-24

[96] de Bruijn AM, Smink M, Hehenkamp WJK, et al. Uterine artery embolization for symptomatic adenomyosis: 7-year clinical follow-up using UFS-Qol questionnaire. Cardiovascular and Interventional Radiology. 2017;**40**(9):1344-1350

[97] de Bruijn AM, Smink M, Lohle PNM, et al. Uterine artery embolization for the treatment of adenomyosis: A systematic review and meta-analysis. Journal of Vascular and Interventional Radiology. 2017;**28**(12): 1629-1642.e1

[98] Dessouky R, Gamil SA, Nada MG, Mousa R, Libda Y. Management of uterine adenomyosis: Current trends and uterine artery embolization as a potential alternative to hysterectomy. Insights Imaging. 2019 Apr 27;**10**(1):48. DOI: 10.1186/s13244-019-0732-8

[99] Alvi FA, Glaser LM, Chaudhari A, et al. New paradigms in the conservative surgical and interventional management of adenomyosis. Current Opinion in Obstetrics & Gynecology. 2017;**29**(4): 240-248

[100] Lefebvre G, Vilos G, Allaire C, et al. The management of uterine leiomyomas. Clinical Practice Gynaecology Committee, Society for Obstetricians and Gynaecologists of Canada. Journal of Obstetrics and Gynaecology Canada. 2003;**25**(5): 396-418; quiz 419-22

[101] Dueholm M. Minimally invasive treatment of adenomyosis. Best Practice & Research. Clinical Obstetrics & Gynaecology. 2018;**51**:119-137

[102] Smeets AJ, Nijenhuis RJ, Boekkooi PF, et al. Long-term follow-up of uterine artery embolization for symptomatic adenomyosis. Cardiovascular and Interventional Radiology. 2012;**35**(4):815-819

[103] Liang E, Brown B, Rachinsky M. A clinical audit on the efficacy and safety of uterine artery embolisation for

symptomatic adenomyosis: Results in 117 women. The Australian & New Zealand Journal of Obstetrics & Gynaecology. 2018;**58**(4):454-459

[104] Marshburn PB, Matthews ML, Hurst BS. Uterine artery embolization as a treatment option for uterine myomas. Obstetrics and Gynecology Clinics of North America. 2006;**33**(1):125-144 Review

[105] Mori T, Nagasawa H. Mechanisms of development of prolactin-induced adenomyosis in mice. Acta Anatomica (Basel). 1983;**116**(1):46-54

[106] Sakamoto A. Subserosal adenomyosis: A possible variant of pelvic endometriosis. American Journal of Obstetrics and Gynecology. 1991;**165**(1): 198-201

[107] Donnez J, Nisolle M, Smoes P, et al. Peritoneal endometriosis and "endometriotic" nodules of the rectovaginal septum are two different entities. Fertility and Sterility. 1996;**66**(3):362-368

[108] Nisolle M, Donnez J. Peritoneal endometriosis, ovarian endometriosis, and adenomyotic nodules of the rectovaginal septum are three different entities. Fertility and Sterility. 1997;**68**(4):585-596

[109] de Bruijn AM, Smink M, Lohle PNM, et al. Uterine artery embolization for the treatment of adenomyosis: A systematic review and meta-analysis. Journal of Vascular and Interventional Radiology. 2017;**28**(12): 1629-1642.e1. Review

[110] Sharara FI, Kheil MH, Feki A, et al. Current and prospective treatment of adenomyosis. Journal of Clinical Medicine. 2021;**10**(15):3410

[111] Mikos T, Lioupis M, Grimbizis GF, et al. The outcome of fertility-sparing and nonfertility-sparing surgery for the treatment of adenomyosis. A systematic review and meta-analysis. Journal of Minimally Invasive Gynecology. 2020;**27**(2):309-331.e3

[112] Soave I, Wenger JM, Pluchino N, et al. Treatment options and reproductive outcome for adenomyosis-associated infertility. Current Medical Research and Opinion. 2018;**34**(5):839-849

[113] Oliveira MAP, Crispi CP Jr, Brollo LC, et al. Surgery in adenomyosis. Archives of Gynecology and Obstetrics. 2018;**297**(3):581-589

[114] Rocha TP, Andres MP, Borrelli GM, Abrão MS. Fertility-sparing treatment of adenomyosis in patients with infertility: A systematic review of current options. Reproductive Sciences. 2018;**25**(4):480-486

[115] Marques ALS, Andres MP, Kho RM, et al. Is high-intensity focused ultrasound effective for the treatment of adenomyosis? A systematic review and meta-analysis. Journal of Minimally Invasive Gynecology. 2020;**27**(2): 332-343

[116] Pyra K, Szmygin M, Szmygin H, Bèrczi V, Kidzinski R, Jargiello T, et al. Endovascular embolization as a treatment for symptomatic adenomyosis—Results of preliminary study. Ginekologia Polska. 2021. DOI: 10.5603/GP.a2021.0136

[117] Kim MD, Kim S, Kim NK, et al. Long-term results of uterine artery embolization for symptomatic adenomyosis. AJR. American Journal of Roentgenology. 2007;**188**(1):176-181

[118] de Bruijn AM, Ankum WM, Reekers, et al. Uterine artery embolization vs hysterectomy in the treatment of symptomatic uterine fibroids: 10-year outcomes from the randomized EMMY trial. American Journal of Obstetrics and Gynecology. 2016;**215**(6):745.e1-745.e12

[119] Gupta JK, Sinha A, Lumsden MA, et al. Uterine artery embolization for symptomatic uterine fibroids. Cochrane Database of Systematic Reviews. 2014;(12):CD005073. Review

[120] Yang W, Liu M, Liu L, et al. Uterine-sparing laparoscopic pelvic plexus ablation, uterine artery occlusion, and partial adenomyomectomy for adenomyosis. Journal of Minimally Invasive Gynecology. 2017;**24**(6): 940-945

[121] Kang L, Gong J, Cheng Z, et al. Clinical application and midterm results of laparoscopic partial resection of symptomatic adenomyosis combined with uterine artery occlusion. Journal of Minimally Invasive Gynecology. 2009;**16**(2):169-173

[122] Peters A, Rindos NB, Guido RS, et al. Uterine-sparing laparoscopic resection of accessory cavitated uterine masses. Journal of Minimally Invasive Gynecology. 2018;**25**(1):24-25

[123] Oliveira MAP, Crispi CP Jr, Brollo LC, et al. Surgery in adenomyosis. Archives of Gynecology and Obstetrics. 2018;**297**(3):581-589

[124] Kwack JY, Kwon YS. Kaohsiung conservative surgery of diffuse adenomyosis with TOUA: Single surgeon experience of one hundred sixteen cases and report of fertility outcomes. Journal of Medical Sciences. 2018;**34**(5):290-294

[125] Chen D, Ai G, Yang W, et al. Laparoscopic uterine artery occlusion combined with uterine-sparing pelvic plexus block and partial adenomyomectomy for adenomyosis: A video case report. Journal of Minimally Invasive Gynecology. 2021;**S1553-4650**(21):00237-00235