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Adenomyosis: Current knowledge, Recent Advances and Future Perspective

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ABSTRACT

Aim: *Adenomyosis is an abnormal overgrowth of the endometrial tissues within the myometrium causing enlargement of the uterus. This present review will focus on clinical symptoms, diagnostic approach, image findings, complications, and management of Adenomyosis. The goal is also to highlight the recent advances in the topic.*

Methodology*: A total of 15 articles published in various journals have been included to write the current review. PubMed, Research Gate, Scopus, Springer are some of the databases used for the literature search.*

Results: *After reviewing the literature Adenomyosis has been discussed under the following topics 1) epidemiology (known and emerging risk factors) 2) Pathogenetic Theories (recent advances such as sequencing analysis of epithelial cells in Adenomyosis) 3) Clinical Manifestations and impact on women's fertility and pregnancy outcome 4)Diagnostic Approach, Current imaging techniques and classifications 5) Medical Management 6) Surgical Interventions (with recent advances such as UAE) 7) Future Perspective.*

Conclusion: *The prevalence of Adenomyosis is still unknown owing to the lack of a validated standard diagnostic approach. Historically, the standard treatment of adenomyosis has been hysterectomy, but this is not always the best option, especially for women who want to preserve their fertility or for those who are poor surgical candidates.*

Keywords
Adenomyosis

Introduction

The term "Adenomyosis" refers to an abnormal growth of the endometrial tissues into the myometrium causing the uterus to enlarge [1] A German pathologist by name Carl von Rokitsansky was the first to describe adenomyosis in the year 1860; and he initially referred it as "adenomyomas". The exact etiology of the condition is unknown. However, recent theories about the pathophysiology of endometriosis can alter our understanding of adenomyosis as well [2]. In some patients, adenomyosis coexists with other gynecological pathologies such as endometriosis and uterine fibroids. Endometriosis is defined as the presence of endometrial glands and stroma-like lesions in the outer surface of the uterus [3] Over the last decade, adenomyosis is mainly identified among young fertile-age women (especially post pregnancy). The most typical clinical manifestations of this disease include pelvic pain, menorrhagia, dysmenorrhea, infertility. However, the frequency and severity of the occurrence of these symptoms and the proportion of adenomyosis sufferers who are completely asymptomatic are unclear [4]. With the emergence of MRI, followed by transvaginal ultrasound (TVUS), the diagnostic approach of adenomyosis has seen an exceptional breakthrough

[5]. Medications such as non-steroidal anti-inflammatory drugs and/or hormonal therapy (oral contraceptives, high dose progestins, danazol, gonadotropin-releasing hormone agonists, a levonorgestrel-releasing intrauterine device) are often used to manage the symptoms [6]. Adenomyosis has never been fully characterized until now since hysterectomy has been the primary therapeutic option worldwide [7]. Minimally invasive surgical techniques (uterine artery ligation, endometrial ablation/resection, myometrial excision/reduction, myometrial electrocoagulation) have limited success in the treatment of adenomyosis, however, latest approaches namely uterine artery embolization (UAE), magnetic resonance imaging guided focused ultrasound (MRgFUS) show promising results in the treatment [8]. There are no standard international guidelines to follow for surgical or medical treatment of adenomyosis. This holds a notable importance in the future, as the disease requires a lifelong management process, fertility preservation and pregnancy outcome [9]. In this paper, current and future trends in the diagnostic approach and management plan would be reviewed.

Epidemiology

In recent years, the diagnosis of adenomyosis was made solely based on histological analysis. Estimates of adenomyosis prevalence vary from 5-70% with the mean incidence of hysterectomy being approximately 20-30% [10]. Gynecological University Clinic in Tubingen conducted a series of consecutive laparoscopic hysterectomies where adenomyosis was histologically diagnosed in 8% of cases (149 out of 1955 women), and associated adenomyosis and leiomyomas was diagnosed in 20% of the women (398 out of 1955 women), 70% of women were premenopausal [7]. There is a wide modification in incidence of adenomyosis between racial and ethnic groups and different geographic regions [11], however one third of the patients with Adenomyosis are asymptomatic. Additionally with an increase in hysterectomy cases performed as laparoscopic supracervical involvement, resulting in uterine specimens, the dimensional arrangement of the tissue is altered, which leads to different reference to the surface and histologically diagnosing adenomyosis becomes difficult. The likelihood of presence of adenomyosis is directly corresponds to the number of tissue samples accumulated with the diagnosis rate ranging from 31-62% in the same uterus [7,10]. In women, undergoing Assisted Reproductive Techniques (ARTs) adenomyosis prevalence is 20-25%, whereas in women with a history of endometriosis the prevalence varies between 20-80% [1].

Risk Factors

Age

70-80% of women who have undergone hysterectomy for adenomyosis are in their 3rd and the 4th decade of life [12]. Currently new reports using MRI imaging for diagnosis suggest that disease may cause symptoms like chronic pelvic pain and dysmenorrhea (menstrual cramps) in adolescents and women of younger fertile age [7,13].

Prior Uterus Surgery

There is no evidential proof to indicate a significant increased risk of prior uterine surgeries in women with adenomyosis [7]. However, according to Yilmaz et al., women with a history of pregnancy termination via dilation and curettage depicted higher rates of adenomyosis as compared to women without any pregnancy termination [14]. Non-pregnant women with a history of dilation and curettage also showed higher incidence rate [7,11]. Women post caesarean section did not demonstrate any marked increase in the rates of adenomyosis [14].

Multiparity

Multiparous women exhibited a marked increase in adenomyosis rates [15]. Occurrence of adenomyosis during pregnancy is generally due to adenomyotic foci which become included in the myometrium. These foci have a higher ratio of estrogen receptors, which pave way for the formation of islands of ectopic endometrium [16].

Ectopic Pregnancy

If the implantation occurs within the focus of adenomyosis, pregnancy can develop within the myometrium [7,14] therefore adenomyosis could also be a risk factor for the development of intramural ectopic pregnancy [18]. Increased likelihood of ectopic pregnancy in association with adenomyosis requires additional evidence.

Depression and Antidepressant use

There is a significant increase in the incidence of adenomyosis with increased risk of depression in women and use of antidepressants. This may be due to irregularities in prolactin dynamics [7,19]. Prolactin is produced by uterine tissues including endometrium, myometrium, and leiomyomas. A functional prolactin receptor is present in the uterus, and it can act as a smooth muscle cell mitogen [20]. Depression may have a similar pathogenic factor with adenomyosis (inflammation).

Tamoxifen Treatment

An increased incidence of adenomyosis has been noticed in women treated with Tamoxifen for breast cancer. It is an antagonist of the estrogen receptor in the breast tissue [21]. The rate of adenomyosis depicted among post-menopausal breast cancer patients treated with Tamoxifen is 3-4 times more than the rate reported for pre- and post-menopausal women [22].

Pathogenetic Theories- insight into Next Generation Sequencing (NGS)

Until now, the exact pathogenesis of adenomyosis was largely unknown. However, currently two new theories are prevailing: "invagination" and "metaplasia" [23]. According to Garcia-Solaris et al. [24] and Layendecker et al. [25] Tissue Injury and Repair Mechanism (TIAR) is the most common theory wherein adenomyosis is an outcome of invagination of the endometrial basalis into the myometrium. The metaplasia theory states that the adenomyotic lesions may originate from the metaplasia of

dislodged embryonic pluripotent Mullerian Rests [24]. High estrogen concentrations, smooth muscle cell hyperplasia and hypertrophy reflect reactive changes secondary to ectopic endometrial proliferation [26]. A latest theory named EMID (endometrial-myometrial interface disruption) has been put forth which revises tissue injury and healing theory. EMID caused by uterine surgeries may lead to iatrogenic adenomyosis later in life [27].

Next-generation sequencing (NGS) studies show that a particular cancer associated gene (KRAS) undergoes mutation causing insufficient PR expression. The KRAS mutation triggers a particular pathway to enhance cell survival and proliferation and is thus linked to progesterone resistance in adenomyosis [28]. NGS technology forms the backbone of all genomic contemporary approaches [28].

Clinical Manifestations of Adenomyosis

Adenomyosis is associated with chronic pelvic pain, dysmenorrhoea (menstrual cramps), menorrhagia (heavy and abnormal uterine bleeding) and dyspareunia (painful sexual intercourse) [7,18,29]. Li et al. investigated 710 premenopausal women with adenomyosis and reported that 4.5% of them did not have any symptoms. The most common and frequent complaint was dysmenorrhea (81.7%) [30], however, the clinical symptoms may vary depending on the patient's age [3,4,7,18,29]. The symptoms of adenomyosis are non- specific and can also be related to conditions such as endometriosis, leiomyomas, dysfunctional uterine bleeding among others [7,18].

Impact on Fertility

Presently, infertility is considered as the most strikingly prominent clinical presentation of adenomyosis, and various theories have been out forth to explain the mechanism behind this [1,7,29]. A probable mechanism behind this could be an abnormal utero-tubal transport leading to infertility. This is due to the anatomical disruption of the uterine cavity but also disturbed uterine peristalsis and sperm transport [31]. A meta-analysis published by Vercellini et al. in 2014 [32] reported miscarriage rates of 31% in women with adenomyosis, and 14.1% in non-infected women. In a multicenter study, Mavrelos et al. depicted that the estimated probability of pregnancy decreased from 42.7% in women with no adenomyosis to 22.9% in those with four ultrasound features and 13% in those with all features of adenomyosis [33]. A recent systematic review and meta-analysis on IVF treatment outcomes in adenomyosis [1,34] included 519 patients with TVUS or MRI diagnosis for Adenomyosis and confirmed the damaging effect of the uterine disease on reproductive outcome. The implantation rate, clinical pregnancy per cycle/per embryo transfer, present pregnancy, and live-birth rate among women with adenomyosis were significantly reduced, wherein miscarriage rate was increased [34,35].

Impact on Pregnancy Outcome

Adenomyosis is considered a reproductive disorder wherein, not only fertility is affected but it has a prominent negative effect on the pregnancy outcome as well. There is an elevated risk of preterm birth (PTB) with an adjusted odds ratio (aOR) being 1.84,95% CI 1.39-3.15 in adenomyotic patients [36]. The results were confirmed in a small cohort study conducted by Mochimaru et al. [37] where women diagnosed sonographically or by MRI before pregnancy, showed an increased risk of cesarean delivery (OR 4.5,96% CI 2.1-9.7), small gestational age (SGA) fetuses (OR 4.3,95% CI 1.8-10.3), postpartum hemorrhage (OR 6.5,95% CI 2.2-19.0) and fetal malpresentation (OR 4.2,95% CI 1.6-10.8). The type of adenomyosis has an impact on pregnancy outcome with high incidence of pregnancy-induced hypertension [1]. The factors, which are responsible for the obstetric complications in adenomyosis could be (i) role of inflammation (ii) elevated myometrial prostaglandin production (iii) altered uterine contractility (iv) intrauterine pressure. All of these increase the risk of preterm birth in women with adenomyosis [38].

Diagnostic Approach

Clinical Examination

The classic feature on physical examination is the "boggy" type enlargement of the uterus. This is due to the increased vascularization from the ectopic endometrial tissue and proliferation of the smooth muscles. The uterus appears to be more tender than usual on examination [39].

Histology

Histological examination of the specimen obtained from hysterectomy is the gold standard for diagnosing adenomyosis [1]. Histologically there is a presence of endometrial stromal and glandular tissue deep within the smooth muscle of the myometrium [39]. This is associated with smooth muscle hyperplasia. There are no universal criteria for the depth of invasion and number of foci to be included in the diagnosis. However, in some cases invasion depth of more than one third is taken into account and in some, greater than 4mm [1]. The architecture of adenomyosis is distinctively different from that of functional endometrium in which the glands are solitary, non-branching and longitudinally arranged [40].

Imaging

The development of imaging techniques (such as TVUS and MRI) has permitted clinicians to make non-invasive diagnosis of adenomyosis in women who are receiving conservative treatment, identifying different phenotypes of the disease [1]. Sonographically adenomyosis is categorized as cystic and non-cystic [40], furthermore cystic adenomyosis is classified as: intrinsic, extrinsic, intramural, and interdeterminate [1].

Transvaginal Ultrasound Sonography (TVUS)

It is the first diagnostic technique since it is widely available, cost-effective with increased accuracy if performed by an expert sonologist. The sensitivity ranges from 65-81% and specificity from 65-100% [42]. The transvaginal scans are 2-dimensional and 3-dimensional, wherein 3D-TVUS is considered more superior to 2D-TVUS. The most common TVUS findings are: heterogeneous

myometrium, myometrial cysts, a globular and/or asymmetric uterus, abnormal myometrial echo texture, poorly-defined margins between the endometrium and myometrium, echogenic linear striations and focal adenomyomas [43]. Currently, a standardized reporting system of ultrasound findings of adenomyosis has been introduced using Morphological Uterus Sonographic Assessment (MUSA) criteria. According to this, the typical ultrasound features to diagnose adenomyosis are: asymmetrical thickening of uterine walls, intra-myometrial cysts hypoechoic islands or both, fan-shaped shadowing of myometrium, myometrial echogenic sub endometrial lines and buds, translational vascularity [1,44].

Linear striations and parallel shadowing give the appearance of a "Venetian blind" or "rain shower" due to the prior mentioned combination of symptomatic features: heterogeneous, coarsened echotexture of the myometrium, and acoustic shadowing where a hyperplastic reaction is caused by the endometrial tissues. Adenomyosis is also sometimes referred to as "cirrhosis of the uterus"; due to the presence of heterogeneity and sub endothelial echogenic nodular and linear striations. This gives an appearance of chronic liver parenchymal disease [45]. A new reporting system was suggested by Van den Bosch et al. which includes description of the disease location (anterior, posterior, left lateral, right lateral and fundal), categorization of the lesion as focal or diffuse, presence or absence of intraregional cysts, myometrial layer involvement, disease extent (<25%, 25-50% and >50% of the uterine volume affected by Adenomyosis) and lesion size [41].

Magnetic Resonance Imaging (MRI)

Pelvic MRI is the preferred choice of diagnosis modality, which provides a detailed classification of adenomyosis. Small field of view T2-weighted images are the most useful, especially sagittal and axial [45]. There is prominent thickening of the junctional zone (JP) which is a clear indicative of an MRI diagnosis for Adenomyosis, however, there may be direct or indirect signs of presence of endometrial glands within the myometrium and the smooth muscle cell hypertrophy [1]. The MRI sequence findings include: (i) T1- foci of high T1 signal are frequently observed, which indicates menstrual hemorrhage into the ectopic endometrial-myometrial tissues (ii) T2- classically a region of adenomyosis presents as an ill-defined ovoid/diffuse region of thickening. Frequently small high T2 signal regions represent small areas of cystic change. The region may also have striated appearance. (iii) T1C+(GD)- MRI evaluation need not be contrast-enhanced for assessment of adenomyosis. However, if performed; it shows enhancement of the ectopic endometrial-myometrial glands [45]. A sensitivity of 46.1%, specificity of 99.2% and a positive predictive value (PPV) is noted in MRI for the diagnosis of adenomyosis. This was described by Stamatopoulos and team in a cohort observational study [46]. The classic MRI findings are the focal or diffuse thickening of the JZ, which is seen as an area of low-signal-intensity in the myometrium and high-signal-intensity spots in the T2-weighted resonance. Bazot et al. reported a sensitivity of 77.5%, specificity of 92.5%, and a PPV of 83.8% in a prospective study with 120 patients. Junctional zone thickness (max) >12mm, a JZ (max) to myometrial thickness ratio > 40% and the presence of high-signal-intensity myometrial spot were the most specific factors, while JZ(max) was the most sensitive value . Normal junctional zone thickness is <8mm [47].

Swiss cheese appearance: It is a type of diffuse adenomyosis that has a "Swiss cheese appearance" with exuberant myometrial cysts and nodules on contrast enhanced and T2 sequences. It is secondary to cross sectional imaging of dilated endometrial glands within the myometrium. There is also a widening and poor definition of JZ and linear striations [48].

Hysteroscopy

This surgical approach favors the direct visualization of the uterine cavity, which gives the option of collecting the histological biopsy samples under visual control [49]. Hysteroscopy shows the following typical findings: irregular endometrium with small openings on the endometrial surface, prominent hypervascularization, and a classic endometrial “strawberry pattern, fibrous and hemorrhagic cystic lesions [50].

Hysterosalpingography (HSG)

It is a type of X-ray procedure, which views the inside of the uterus and fallopian tubes. It depicts the presence or absence of blockage in the tubes and evaluates the normal size and shape of the uterus. In 1949, the first report was published about using hysterosalpingography (HSG) to diagnose adenomyosis, however, due to its low sensitivity, HSG was never utilized as a prime diagnostic tool [51]. Adenomyosis is seen as irregular branching outpouching radiating from the uterine cavity; representing extension of the endometrial glands of the myometrium [52].

Management

Medical treatment

Medical treatment is the first line of treatment option for adenomyosis. This helps relieve symptoms and maintain fertility with significantly less side effects. The mechanism involves the disruption of the pathways, which lead to inflammation, neuroangiogenesis, and impaired apoptosis. Presently, various hormonal and non-hormonal options, namely gonadotropin-releasing hormone (GnRH) analogues, selective estrogen receptor modulators (SERMs), aromatase inhibitors (AIs), selective progesterone receptor modulators (SPRMs), combined oral contraceptive, and non-steroidal anti-inflammatory drugs are being used for the symptomatic treatment of adenomyosis [53]. Newer drugs, such as aromatase inhibitors, have also been investigated by Badawy et al. and Rosti et al, while other therapies such as selective progesterone receptor modulators, GnRH antagonist, valproic acid, and antiplatelet therapies are still under investigation [54]. Among progestins, norethisterone acetate (NETA), vaginal danazol, and dienogest (DNG) may be considered [1].

The levonorgestrel-releasing intrauterine system (LNG-IUS) is an effective, reversible, and long-term treatment, which is successfully used to treat adenomyosis. Results show reduced

menstrual bleeding, pain and uterine volume and have an overall satisfaction of 72% [55].

Minimally Invasive Techniques

This is a second line of treatment modality after a failed medical treatment, which allows the patient to retain their uterus. Excisional adenomyomectomy involves the complete extraction of the focal lesions (adenomyomas), while myomectrectomy is the surgical debulking of diffuse adenomyosis. Non-excisional treatments aim to induce necrosis of focal or diffuse adenomyosis through selective vascular occlusion or focused ultrasound/thermal energy without direct tissue dissection. In some cases, a combination of surgical and non-excisional methods, i.e., hysteroscopy resection/ablation, are used to achieve maximum cytoreduction and reduce myometrial tissue damage [53].

Conservative Surgical Treatment

The first report of a conservative surgical treatment for adenomyosis in young women was reported in the year 1952. The partial excision of an adenomyosis, as a cytoreduction surgery, became common in which the uterine wall is excised in a V-shape [56].

Several laparotomic techniques have been described, which includes the following:

Wedge Resection technique - In this approach, parts of serosa and uterine adenomyomas are excised via wedge resection after identifying the parts of the neuromuscular layer where the adenomyoma is located. The uterine wall wound is sutured together with the remaining muscular layer and serosa [57].

Modified Resection technique- first reported in 1991, this involves the cutting of the adenomatous tissue into thin slices using a microscopic technique in conjunction with laparotomy surgery [58].

Transverse H Incision of uterine wall -in this procedure the transverse incision is made on the uterine fundus, using an electro-surgical scalpel, separating the uterine serosa from the uterine myometrium. The adenomyoma tissue is removed using the electro-surgical scissors or scalpel.

Wedge-shaped Uterine wall removal- here the adenomyoma is resected with a thin margin (wedge shaped removal) after a sagittal incision in the uterine body. The radical resection involves the laminate layers on both the endometrial and serosal sides. The suturing technique used is the “baseball” or “continuous Lembert stitch method” [58].

Triple flap method- This method involves reconstructing the uterine wall defect using normal uterine muscle. It has three characteristics: complete extraction of the uterine adenomyosis by performing adenomyomectomy; reconstruction of a uterine cavity, which can sustain future pregnancy (here an endometrial uterine muscle flap is prepared by metroplasty through opening the uterine cavity and removing the uterine adenomyosis under palpation); and reconstruction of a uterine wall resistant to rupture during a subsequent pregnancy [58].

Laparoscopic techniques have also been described in more focal pathology [53]. Laparoscopic adenomyomectomy with hysteroplasty-_transverse incision is made in the adenomyotic tissue down to the endometrium. The diseased tissue is surgically removed using a monopolar needle. The normal muscle layer on the serosal membrane side is left as an upper and lower serosal flap. The flaps are overlapped and sutured to counteract the lost muscle layer to reconstruct the uterus [59].

The main issue with conservative surgical methods is the high risk for complications, i.e., uterine rupture and complicated pregnancy (especially in diffuse lesions and on long-term follow-up), making this option safer in focal adenomyomas [53].

Hysteroscopy resection/ablation

This is a combined method, which involves the dissection or coagulation of cystic adenomyotic lesions and crypts. It can be performed using yttrium aluminum garnet (YAG) laser, cryoablation, circulated hot fluid ablation, microwave ablation, roller ball resection, thermal balloon resection, electrocoagulation, bipolar radiofrequency ablation [7].

High-Intensity Focused Ultrasound (HIFU)

This was first introduced in the year 1942 by Lynn et al. Intense ultrasound energy is used directly which targets the abnormal tissues and their vascularity through heating and cavitation. The normal surrounding tissues are however spared. The method is guided and monitored through MRI or ultrasound [60]. HIFU has been used in the treatment of adenomyosis since 2008 [53]. Recent studies have investigated the use of ultrasound contrast agents (microbubbles) and hormonal (GnRH) and non-hormonal (Metformin) treatments, which enhance the HIFU efficiency. Microbubbles improve the ablative effects of HIFU by changing acoustic characteristics while GnRH and Metformin inhibit cellular proliferation and induce apoptosis [61]. This technique is not commonly used compared to other minimally invasive methods due to limited availability, overall cost, unknown fertility outcome and strict biological indicators [53].

Uterine Artery Embolization (UAE)

This is a method, which uses Trans arterial catheters which aims to induce more than 34% necrosis within the adenomyotic tissues [53]. In 1995, the first paper was published by Ravin et al., Which reported a woman being treated by the UAE for symptomatic uterine leiomyomas. The procedure is performed under local anesthesia using the right femoral artery puncture approach. Selective digital subtraction angiography is performed to evaluate the hypogastric and uterine arteries. Embolization is performed through the microcatheter using non-spherical PVA particles. The end point of embolization is complete stasis of blood flow in the uterine artery [62]. A study conducted by Popovic et al,

Treatment		Mechanism
Type		
Non-Surgical	Gonadotropin-Releasing hormone (GnRH) Analogues *(53) Dessouky 2017*	Endometrial atrophy, Hypoestrogenism
	Selective estrogen receptor modulators (SERMs) *(53) Dessouky 2017*	Differential ER expression in target tissue
	Aromatase inhibitors (AIs) *(53) Dessouky 2017*	Inhibition of estradiol synthesis (suicidal/ competitive)
	Selective progesterone receptor modulators (SPRMs) *(53) Dessouky 2017*	Differential PR expression in target tissue
	Combined oral contraceptive *(53) Dessouky 2017*	Atrophy of endometrial tissue causing decreased menstrual bleeding
	Non-steroidal anti-inflammatory drugs (NSAIDs)	Decreased pain and abnormal bleeding due to decreased prostaglandins
	Norethisterone acetate (NETA)	Decidualization and atrophy of endometrial tissue
	Vaginal danazol *(1) Vannucini 2019*	Hyperandrogenism
	Dienogest (DNG) *(1) Vannucini 2019*	Suppression of estradiol
	Levonorgestrel-releasing intrauterine system (LNG-IUS) *(55) Sheng 2009*	Mediated through slow-release progestin
Surgical		
Conservative	Wedge Resection *(57) Nishida 2007*	Parts of serosa and uterine adenomyomas are excised
	Modified Resection technique *(58) Osada H 2018*	Involves the cutting of the adenomatous tissue into thin slices
	Transverse H Incision of uterine wall *(58) Osada H 2018*	Transverse incision was made on the uterine fundus
	Wedge-shaped Uterine wall removal *(58) Osada H 2018*	Adenomyoma is resected with a thin margin
	Triple flap method	Involves reconstructing the uterine wall defect using normal uterine muscle
	Laparoscopic adenomyomectomy with hysteroplasty *(59) Takeuchi H 2006*	Transverse incision is made in the adenomyotic tissue down to the endometrium.
Minimally Invasive	Hysteroscopic resection/ablation *(7) Taran FA 2013*	Dissection or coagulation of cystic adenomyotic lesions and crypts
	High-intensity focused ultrasound (HIFU) *(53)Dessouky R 2017, (60) Cheung VY 2017, (61) Hou Y 2018*	Intense ultrasound energy is used which targets the abnormal tissues
	Uterine artery embolization (UAE) *(53) Dessouky 2017, (62) Yuan K 2021, (63) Popovic M 2011*	Trans arterial catheters which aim to induce more than 34% necrosis within the adenomyotic tissues

demonstrated long term improvement in patient symptoms (in over 60% of patients) and a short-term decrease in uterine volumes (in over 20% of patients) especially in vascular lesions [63]. Results of an ongoing randomized controlled (QUESTA) trial will soon prove the validity of UAE as a treatment option for adenomyosis [53].

Future Perspective

Over the next 5-10 years, ultra-long regulation protocols will be preferred during IVF/ICSI cycles for women with suggestive symptoms or signs of adenomyosis. The diagnosis for adenomyosis should be standardized according to an internationally approved criterion. Significant consequences of Adenomyosis such as preterm birth, spontaneous miscarriage, intrauterine growth retardation, preeclampsia, eclampsia, obstetrical hemorrhages, placental bed, and adherence abnormalities should be evaluated with well-assessed studies [64].

Conclusion

There has been a significant improvement in the understanding and management of adenomyosis in recent years. It has become a clinical entity rather than a histological diagnosis, which can be identified through various non-invasive imaging techniques. An increasing amount of evidence suggests the improvement in the treatment modalities owing to minimally invasive techniques, however, there is still a need for a uniform diagnostic criteria profile and reporting system, in order to identify all the clinical and imaging phenotypes of adenomyosis. Clinicians are required to conduct prospective studies on adenomyosis prevalence, effective medical or surgical treatments and impact on fertility and pregnancy outcomes.

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