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Narrative Review

Comprehensive Overview of Adenomyosis: Pathogenesis, Clinical Presentation, Diagnosis, and Management - A Narrative Review

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Abstract

Adenomyosis, characterized by the presence of ectopic endometrial tissue within the myometrium, presents a significant clinical challenge due to its various manifestations and major impact on women's health. This narrative review provides a comprehensive overview of adenomyosis, focusing on its pathogenesis, clinical presentation, diagnosis, and management. The pathogenesis of adenomyosis involves intricate interactions between hormonal, and environmental factors, leading to the invasion of endometrial tissue into the myometrium. Various hypotheses, including metaplasia, invagination, and stem cell theory, have been proposed to understand adenomyosis development. Adenomyosis presents with a variety of symptoms, including dysmenorrhea, menorrhagia, pelvic pain, dyspareunia, and infertility. The variability in symptomatology highlights the importance of a multidisciplinary approach to diagnosis and management. Accurate diagnosis of adenomyosis is achieved by a combination of clinical history, physical examination, and imaging modalities. Transvaginal ultrasound and magnetic resonance imaging (MRI) are commonly used for detecting adenomyotic lesions, although challenges remain in standardizing diagnostic criteria and differentiating adenomyosis from other uterine pathologies. Treatment strategies for adenomyosis aim to alleviate symptoms, preserve fertility, and improve quality of life. Medical management includes analgesics, hormonal therapies, and aromatase inhibitors. Surgical interventions, including adenomyomectomy and hysterectomy, may be considered for individuals seeking definitive treatment. Future research directions in adenomyosis should prioritize further clarifying its pathogenesis, identifying biomarkers for early detection and prognosis, and developing targeted therapies. Standardization of diagnostic criteria, optimization of imaging techniques, and multidisciplinary approach are essential for advancing research on adenomyosis and improving patient care. In conclusion, this narrative review provides a comprehensive overview of adenomyosis, highlighting its complex pathogenesis, clinical presentation, diagnostic challenges, and management strategies.

Keywords: *Magnetic Resonance Imaging (MRI); Adenomyosis; Stem Cell Theory*

Introduction

Definition, historical context and significance

Adenomyosis, a benign gynecological disorder characterized by the ectopic presence of endometrial glands and stroma within the myometrium, as depicted in figure 1. This disorder has undergone a notable transformation in both its conceptualization and clinical significance over the past century [1]. Originally described in 1947 by Hunter., *et al*. adenomyosis was primarily identified through

histopathological examination of uterine specimens obtained during surgical procedures, particularly hysterectomies [2]. The defining histological feature of adenomyosis involves the infiltration of endometrial glands and stroma into the myometrial layer, often accompanied by smooth muscle hyperplasia. However, in recent decades, adenomyosis is no longer considered a mere histological finding. It is a clinically relevant condition, diagnosed increasingly through non-invasive imaging techniques such as transvaginal ultrasound (TVUS) and magnetic resonance imaging (MRI) [3]. This shift has broadened our understanding of adenomyosis beyond its historical association with older, multiparous women undergoing hysterectomy for heavy menstrual bleeding (HMB) [4]. The significance of adenomyosis in current gynecology is highlighted by its inclusion as a specific item in the PALM-COEIN FIGO classification system for causes of abnormal uterine bleeding (AUB), highlighting its clinical relevance in the context of women's health. Moreover, adenomyosis frequently coexists with other gynecological conditions such as endometriosis and uterine fibroids, suggesting potential shared pathogenic mechanisms and clinical implications [5].

The history of adenomyosis dates back to the 19th century. Karl von Rokitansky was one of the first to describe glandular structures embedded in the uterine myometrium [6]. Initially named "cystosarcoma adenoids uterinum", this condition was later termed Adenomyosis. Other researchers, like Chiari, also made significant observations. Chiari proposed the concept of "salpingitis isthmica nodosa" as a variant of adenomyosis [7]. In the late 19th century, Meyer introduced the theory of "epithelial heterotopy", suggesting that epithelial cells could invade damaged inflammatory tissue, contributing to Adenomyosis [8]. Cullen made substantial contributions by systematically describing Adenomyosis and linking its pathology to clinical symptoms like pelvic pain and prolonged menstrual periods. He supported hysterectomy as the preferred treatment due to the challenges of dissecting out adenomyomas. However, Cullen's theory faced opposition from modern theories proposing different mechanisms, including displacement of mesonephric components and idiopathic stromal hyperplasia [9]. It wasn't until the 1920s that the endometrial origin of adenomyosis gained widespread acceptance, coinciding with Sampson's theory of worsening menstruation [10]. The term "adenomyosis uteri" was introduced by Frankl in 1925, emphasizing the invasion of the myometrium by endometrial tissue and differentiating adenomyosis from inflammatory processes [11]. In 1972, Bird., *et al.* established the modern histological definition of adenomyosis, characterizing it as the benign invasion of endometrium into myometrium, leading to a diffusely enlarged uterus with ectopic endometrial glands and stroma surrounded by hypertrophic and hyperplastic myometrium [12].

Despite its long-standing recognition, the etiology of adenomyosis remains elusive, with various theories proposed to explain its development. These include the invagination of basalis endometrium into the myometrium or *de novo* metaplasia of embryonic Müllerian remnants. The lack of a unified pathogenic model and inconsistencies in diagnostic criteria and classifications, presents as a significant challenge in establishing a standardized definition of adenomyosis [13].

Beyond diagnostic and pathogenic complexities, adenomyosis exerts a significant impact on women's quality of life, including several symptoms ranging from heavy menstrual bleeding, dysmenorrhea and pelvic pain to infertility and even asymptomatic presentations. Furthermore, emerging evidence suggests associations between Adenomyosis and adverse obstetrical outcomes, as well as potential links to other non-malignant chronic conditions and increased cancer risks [14]. Due to these multifaceted considerations, a comprehensive understanding of Adenomyosis is vital for healthcare professionals and researchers. Efforts to explain its pathogenesis, refine diagnostic criteria, and optimize therapeutic approaches are essential to address the diagnostic challenges, clinical management, and broader public health implications associated with this complex gynecological condition [15].

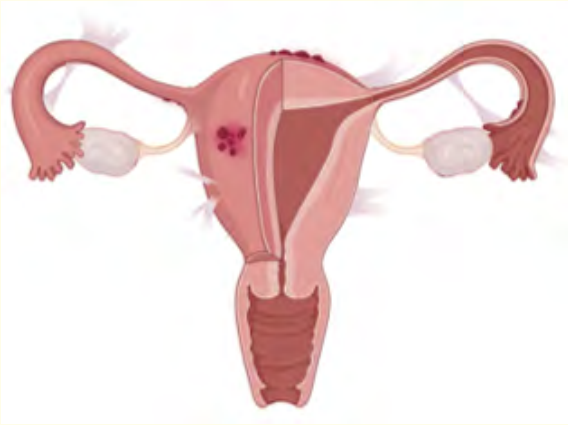

Figure 1: *Adenomyosis [1].*

Epidemiology

The accurate prevalence of adenomyosis, which refers to the proportion of a specific population with the condition at a given time, remains uncertain [16]. This uncertainty is due to the reliance on histopathological examination of uterine tissue post-hysterectomy as the gold standard for diagnosis, leading to prevalence estimates being derived only from a selected group of women undergoing this major surgery i.e. hysterectomy [17]. These women typically have severe symptoms impacting their quality of life, which may not have responded to conservative treatments or other surgical interventions. Prevalence estimates among women undergoing hysterectomy have varied widely over the past five decades, ranging from 8.8% to 61.5% [18]. This variability can be attributed to several factors, including differences in histopathologic diagnostic criteria, variation in the number of tissue samples evaluated per hysterectomy, and variations in awareness among healthcare providers. The use of different diagnostic criteria has also further contributed to this variability, with prevalence estimates varying based on the strictness of the diagnostic criteria applied [19]. The reliance on hysterectomy for diagnosis has also hindered the assessment of adenomyosis prevalence by age. Since hysterectomy studies include women across a wide age range, from young to elderly, the median age at surgical diagnosis typically falls between 40 and 50 years [20]. This age distribution reflects the peak incidence of hysterectomy, which occurs among women aged 40 to 49 years. Consequently, the common perception that adenomyosis primarily affects older reproductive-age women, based on hysterectomy data, may overlook and underestimate its occurrence in younger women [21]. Overall, limitations in diagnostic methods and study populations hinder our understanding of adenomyosis prevalence, emphasizing the need for further research to accurately assess its occurrence across different demographics and to better inform clinical management strategies [22].

To date, systematic screening for adenomyosis using imaging techniques has not been conducted in the general population. However, several studies have investigated the prevalence of adenomyosis among women referred by healthcare providers for transvaginal ultrasound (TVUS) [23]. One study, conducted in a general UK gynecology clinic, included 985 women undergoing TVUS for various indications such as menorrhagia, pelvic pain, infertility, irregular bleeding or amenorrhea, and postmenopausal bleeding. In this population, the prevalence of adenomyosis was found to be 20.9% [24]. A subsequent study within the same population, specifically focusing on premenopausal women with recent menstruation, reported a slightly higher prevalence of 21.9% [25]. Another study conducted in Italy targeted nulligravid women aged 18-30 attending a gynecology clinic for contraceptive care and referred for ultrasound evaluation. This study employed strict inclusion criteria, including regular menstrual cycles, no use of hormonal medications affecting menstruation,

and no history of infertility or sonographic evidence of endometriosis or leiomyomas [26]. Among the 156 women in this study, the prevalence of adenomyosis was notably higher at 34%, with a mean age of adenomyosis cases being 26 years. These findings suggest that adenomyosis may be common and can manifest early during the reproductive years [26,27].

However, similar to histological diagnosis, there is a lack of consensus on imaging diagnostic criteria for adenomyosis, which could affect prevalence estimates. Additionally, the diagnostic quality of imaging modalities may be influenced by hormonal or gonadotropin releasing hormone (GnRH) treatments, and the detection of adenomyosis by TVUS can also be dependent on the operator [28]. Despite these challenges, recent advancements in noninvasive imaging methods, such as TVUS and MRI, have facilitated the detection of adenomyosis outside the context of hysterectomy. A systematic review and meta-analysis of high-quality studies revealed that TVUS and MRI comparably perform reasonably well in diagnosing adenomyosis, with reported sensitivity and specificity values [29]. These advancements in imaging technology offer a promising future for improved detection and diagnosis of adenomyosis in clinical practice.

The diverse range of adenomyosis prevalence estimates from hysterectomy and imaging studies has not provided a clear understanding of its prevalence among women with various other uterine-related conditions, including leiomyomas, pelvic organ prolapse, menorrhagia/abnormal uterine bleeding, infertility, and endometriosis [30]. Among women with leiomyomas, the reported prevalence of adenomyosis varies widely, ranging from 16% to 62% in women undergoing hysterectomy or other surgical interventions. Similarly, the prevalence of adenomyosis among women with pelvic organ prolapse ranges from 20% to 31%, while for those experiencing menorrhagia/abnormal uterine bleeding, it varies between 26% and 49% [31].

Studies evaluating adenomyosis frequency among women with infertility have reported prevalence rates of 8% to 24% using TVUS. Among women with endometriosis, the prevalence of adenomyosis also shows significant variability [33]. Histopathological diagnosis during surgery has yielded prevalence rates ranging from 15% to 31% [34]. However, prevalence estimates based on imaging techniques such as TVUS and MRI range from 22% to 89% and 27% to 65%, respectively [35].

Moreover, higher prevalence rates of adenomyosis have been observed among women with endometriosis who experience concurrent infertility or pelvic pain/dysmenorrhea, with rates ranging from 35% to 79% and 38% to 87%, respectively. The 2 disorders are characteristically different as summarized in table 1 [36]. When focused on women with deep infiltrating endometriosis, adenomyosis prevalence is found to be notably high, ranging from 35% to 78% [37]. Focal adenomyosis of the outer myometrium exhibits the highest reported prevalence, ranging from 49% to 97% [38]. These findings highlight the complex relationship between adenomyosis and other uterine-related conditions, emphasizing the need for further research to clarify underlying mechanisms and optimize diagnostic and treatment strategies for affected individuals.

Adenomyosis	Endometriosis
Presence of endometrial glands and stroma inside the myometrium	Presence of endometrial glands and stroma outside the uterus
Glands and stroma are derived from Endometrium Basalis	Glands and stroma are derived from Endometrium Functionalis

Table 1: *Characteristic differences between adenomyosis and endometriosis.*

Risk factors

Several factors have been studied as a potential risk factor for adenomyosis. The most important ones are mentioned in figure 2. Race/ethnicity has not been extensively studied in relation to adenomyosis, but two U.S. studies have provided contradictory findings. One study

involving a large cohort of female teachers in California found a higher prevalence of surgically-confirmed adenomyosis among Latinas compared to white women. However, the number of cases among non-white women were limited, making it difficult to assess associations with other racial or ethnic groups [39]. Conversely, a study in New York among women undergoing hysterectomy found that black women were more likely to have both adenomyosis and leiomyomas compared to Hispanic women [40]. Regarding education, it is suggested as a potential social determinant of health, with higher educational attainment linked to better access to healthcare and resources. However, studies investigating the association between education and adenomyosis risk among women undergoing hysterectomy have produced conflicting results [41]. One study in Italy suggested a lower risk of adenomyosis with higher education, while another study in multiple Italian hospitals indicated an increased risk with greater education [42].

Age at menarche has been proposed as a potential risk factor for adenomyosis, with earlier menarche potentially increasing the risk due to prolonged exposure to estrogen and earlier reproductive system development [43]. However, epidemiologic studies among women undergoing hysterectomy have not consistently supported this hypothesis, with most of the studies reporting no significant association. One exception to the rule is a large study of female teachers in California, which found that menarche at or before age 10 was associated with a 59% increased prevalence of surgically-confirmed adenomyosis [44]. Regarding menstrual cycle frequency, shorter cycles have been linked to increased exposure to estrogen, aligning with the role of hyper-estrogenism in adenomyosis risk [45]. Furthermore, two studies reported greater adenomyosis risk with shorter menstrual cycles. One study among women undergoing hysterectomy found a decreased risk of adenomyosis with menstrual cycles of 26-30 days or ≥ 31 days compared to cycles of ≤ 25 days [46]. Similarly, a prospective cohort study from the California Teachers Study reported a 46% increased prevalence of surgically-confirmed adenomyosis among participants with menstrual cycles ≤ 24 days compared to those with cycles of 27-28 days [47]. However, another study found no association when defining lifelong irregular menstrual cycles as ≤ 21 days or ≥ 32 days in length [48].

Breastfeeding is associated with the absence of ovulatory cycles and estrogen deficiency, suggesting a potential link to a reduced risk of adenomyosis among parous women. In a cohort study conducted among California teachers, parous women who breastfed had a lower prevalence of surgically-confirmed adenomyosis compared to those who did not breastfeed [49]. Regarding menopause, premenopausal and perimenopausal women are generally considered to be at increased risk for adenomyosis due to higher circulating estradiol levels. This was supported by findings from a large cohort of female teachers in California, where premenopausal and perimenopausal women had a higher prevalence of surgically-confirmed adenomyosis compared to postmenopausal women not using hormone therapy [50]. Interestingly, postmenopausal women using various hormone therapies, including estrogen-only preparations, combined estrogen and progestin preparations, and mixed preparations, also had a greater prevalence of adenomyosis diagnosis. However, there are some discrepancies in the literature regarding the association between menopause and adenomyosis risk [51].

Gravidity and parity have been extensively studied as risk factors for adenomyosis, with most studies among hysterectomy patients reporting a positive association between parity and adenomyosis. However, some studies did not find such an association, particularly those including the method of delivery (cesarean delivery), which could affect the results [52]. The leading indication for hysterectomy being leiomyomas, which are associated with parity, raises concern about bias contributing to the observed positive association. However, studies using population-based sampling observed a positive association between parity and adenomyosis [53]. Few studies have investigated gravidity as a risk factor, but all observed a positive association with adenomyosis [54]. Spontaneous and induced abortions, as well as other pregnancy-related procedures like evacuation and dilatation and curettage (D&C), have been studied in relation to adenomyosis. Results have been mixed, with some studies reporting strong, positive associations while others reported null associations [55]. The increased risk of adenomyosis observed with induced abortion may be attributed to trophoblast invasion with pregnancy rather than the D&C procedure itself, especially considering the decline in the use of sharp curettage for terminating pregnancies in the U.S. since the mid-1970s [56]. Studies on the association between cesarean delivery and adenomyosis have generally reported no significant association, despite the expectation that this surgical procedure, involving both trophoblast invasion of pregnancy and surgery, might increase the risk of adenomyosis [57].

Studies investigating the association between oral contraceptive (OC) use and Adenomyosis have generated mixed results. While two studies among women undergoing hysterectomy found no significant association between ever using OCs and Adenomyosis, a large population-based cohort study of teachers in California reported a 54% greater prevalence of surgically-confirmed Adenomyosis among past OC users [58]. However, current OC use at baseline was not associated with Adenomyosis prevalence in this study. Similarly, investigations into the history of intrauterine device (IUD) use did not reveal any association with adenomyosis, according to the same two hysterectomy studies that examined OC use [59].

Tamoxifen, a medication with both anti-estrogenic and weakly estrogenic properties, has been associated with endometrial carcinoma and other uterine pathologies [60]. While no studies evaluated tamoxifen use in relation to adenomyosis, case reports and small studies have suggested a potential link. For example, postmenopausal women treated with tamoxifen exhibited a higher frequency of adenomyosis compared to those not receiving treatment. However, these studies did not fully take into account potential confounding factors, such as parity, which could influence the observed association [61].

Evidence regarding the relationship between estrogens and body fat distribution is growing, but only BMI has been evaluated in adulthood with context to Adenomyosis. However, BMI doesn't reflect fat distribution [62]. Population-based studies have indicated a positive correlation between higher BMI and adenomyosis prevalence, suggesting a possible link. Cigarette smoking, known to impact estrogen levels and age at menopause, initially showed a decreased risk of Adenomyosis but subsequent studies haven't confirmed this. Environmental chemicals like phthalates, which disrupt hormonal action, are possible risk factors [63].

Regarding heritability and genetic risk, no twin studies or genome-wide association studies (GWAS) have been conducted for Adenomyosis. The challenges of studying genetic factors include potential biases when limited to women undergoing hysterectomy, making it difficult to distinguish genes associated with Adenomyosis from those linked to common hysterectomy indications. Further research, especially broader population-based studies, are needed to elucidate the genetic background of Adenomyosis [64].

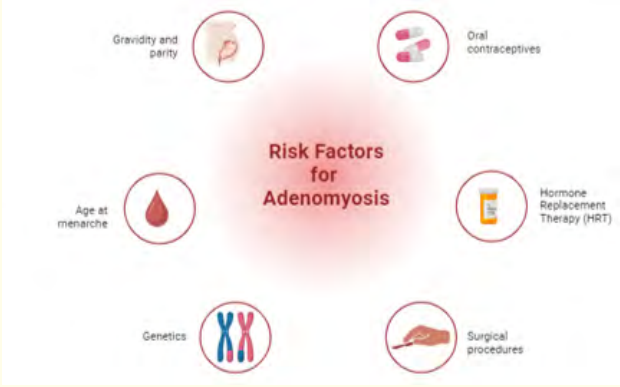

Figure 2: *Risk factors investigated for adenomyosis [43-64].*

Pathogenesis

The pathology of Adenomyosis reveals distinct features that help to distinguish it from other uterine conditions. Grossly, Adenomyosis may cause slight enlargement of the uterus, often appearing slightly globular due to myometrial hypertrophy [65]. Unlike leiomyomas, Adenomyotic foci lack a well-demarcated border and may manifest as indistinct masses with brown-staining areas indicative of hemolyzed

blood and hemosiderin deposits. Adenomyosis can also form localized nodules known as adenomyomas, which lack encapsulation and are composed of hypertrophied myometrium mixed with endometrial glands and stroma [66].

Microscopically, Adenomyosis is characterized by irregularly shaped islands endometrial glands and stroma within the myometrium as depicted in figure 3, often interconnected and resembling the basalis layer of eutopic endometrium. These may vary in size and shape. Some form cystic structures filled with cellular debris and hemosiderin-laden macrophages [67]. Stromal components of Adenomyosis typically present as inactive and non-mitotic. Occasionally, secretory changes are observed during gestation or progestin therapy [68].

The junctional zone between the endometrium and inner myometrium is often thickened in Adenomyosis, exhibiting architectural changes such as smooth muscle hypertrophy and loss of nerve fibers. Structural abnormalities in myocytes associated with Adenomyosis suggest a role in abnormal uterine peristalsis, although the exact mechanisms remain uncertain [69]. Adenomyotic lesions also display a higher angiogenic potential, with increased levels of vascular endothelial growth factor (VEGF) and hypoxia-inducible factor-1α (HIF-1α) compared to eutopic endometrium [70].

These pathological features can be associated with imaging findings such as sub endometrial echogenic linear striations, nodules, and asymmetrical myometrial bulkiness observed in ultrasound or MRI studies. Hyperechoic islands and sub endometrial cysts seen in imaging may reflect focal cystic dilatation of glands within [71] Adenomyosis. Increased vascularity and tortuous vessels on color Doppler sonography are associated with enhanced angiogenesis in adenomyosis. Thickening of the junctional zone, visualized as a hypoechoic halo beneath the endometrial layer, is suggestive of Adenomyosis [72].

Hyperplastic changes, with or without atypia, are common in Adenomyosis and can often be observed in the corresponding eutopic endometrium. However, malignant transformation of Adenomyosis is rare, occurring mostly in postmenopausal women [73]. The most common histological type of malignant transformation is endometrioid carcinoma, although serous carcinoma, clear cell carcinoma, and poorly differentiated carcinoma may also occur. Pathological findings suggesting malignant transformation include the presence of cancerous tissue and ectopic endometrial tissue in the same lesion, evidence of transformation between benign and malignant gland structures, and the exclusion of other sources of tumor invasion or metastasis [74]. In rare cases, stromal cells within Adenomyosis may undergo neoplastic transformation to form intramural adenosarcoma [75].

Other unusual subtypes of Adenomyosis include Adenomyomas, which are nodular forms involving myometrium focally, distinguishing them from the diffuse appearance of commonly observed Adenomyosis. Both Adenomyomas and diffuse types of Adenomyosis may coexist in the same specimen. Salpingitis isthmica nodosa (SIN), once considered as a variant of Adenomyosis, is now primarily viewed as an acquired fallopian tube lesion analogous to Adenomyosis of the uterus [76]. Grossly, SIN appears as nodular protrusions on the tubal serosa, typically localized to the isthmic part of the tube. SIN can cause infertility due to luminal obstruction or tubal pregnancy due to irregular tube lumens. Adenomyosis and SIN may share pathogenic mechanisms, as they both exhibit glandular proliferation with associated muscular hypertrophy [77].

Classification systems for adenomyosis based on histological features have been proposed, including those focusing on the depth of myometrial involvement, the location of adenomyotic lesions, and whether the myometrial involvement is diffuse or localized. However, a standard and widely accepted system for histological classification has not been established, partly due to the lack of significant results when attempting to correlate pathological features with clinical presentations. This may be due to inconsistencies in how specimens are processed and examined, as well as variations in the lesions [78]. Many classification systems have been proposed based on the depth of glands within the myometrium. For example, one system characterized superficial adenomyosis as glands within 40% of the myometrial thickness, intermediate adenomyosis when glands were present in 40 to 80% of myometrial thickness, and deep adenomyosis when glands were seen beyond 80% of the myometrial thickness [79]. Another system applied one-third and two-thirds as the cutoff. However,

these cutoffs are often subjective and lack clinical rationale [80]. Conflicting results arise from studies correlating disease symptoms with the depth of glands within the myometrium. Some studies found a positive correlation between the depth of adenomyosis involvement and symptoms like dysmenorrhea, while others found no correlation. Dysmenorrhea has been correlated with the number of glandular tissue foci within the myometrium, while dyspareunia is associated with the number of lesion foci but not with depth [81]. Diffuse adenomyosis has been associated with worse dysmenorrhea, while focal disease has been linked to infertility, especially when located in the outer myometrium. Menorrhagia has been found to be more prevalent in women with deep adenomyosis compared to those with intermediate disease, and menorrhagia was also found to be more frequently present in the diffuse type of adenomyosis compared to other types based on gross appearance and tissue consistency at the time of surgery [82].

Understanding the pathogenesis of adenomyosis, including the mechanisms by which normal endometrial tissue infiltrates the myometrium and the reasons behind symptomatic manifestation, remains largely vague [83]. Recent histopathological and molecular genetic studies suggest that adenomyosis originates from the basal layer of the endometrium, a concept indicated by Cullen's proposal nearly a century ago. Histological examination of adenomyotic lesions typically reveals irregularly shaped interconnected endometrial glands within stroma, resembling the labyrinthine network in the basal layer of the endometrium [84].

While the favored model for adenomyosis involves the invagination of the endometrial basalis into the myometrium, other theories exist. These include metaplasia of displaced embryonic pluripotent Müllerian remnants or differentiation of adult endometrial progenitor cells [85]. Recent studies on stem cells in the endometrium basalis have suggested they may distribute and cause adenomyosis or endometriosis, potentially due to tissue injury activating stem cells and favoring migration to the myometrium [86]. However, challenges remain, such as how individual stem cells could differentiate into both epithelium and stroma, and the need for further evidence to support these hypotheses. From a histopathological standpoint, it's more plausible that endometrial epithelial progenitor cells reside in basal glands, extending into the myometrium and co-developing with stromal progenitor cells into adenomyosis lesions [87].

Figure 3: *Adenomyosis characterized by endometrial glands and stroma inside myometrium.*

Clinical presentation

Traditionally, menorrhagia and dysmenorrhea have been regarded as the hallmark symptoms of Adenomyosis. However, earlier studies, primarily conducted among cases diagnosed at hysterectomy, raised doubts about adenomyosis as the sole reason for symptoms. In these

studies, approximately one-third of patients were categorized as asymptomatic [88]. A recent study of 710 premenopausal adenomyosis cases diagnosed by hysterectomy, only 4.5% reported none of the four main complaints: dysmenorrhea, menorrhagia, chronic pelvic pain, or metrorrhagia, also referred to as Intermenstrual bleeding as summarized in figure 3 [89].

Since menorrhagia and dysmenorrhea are common to other uterine pathologies that can also lead to hysterectomy, adenomyosis is often described as lacking symptoms specifically characteristic of the disease. Recent studies among patients undergoing transvaginal ultrasound (TVUS) as part of diagnostic work-up have also reported symptoms such as heavy menstrual bleeding, menstrual pain. Additionally, beyond classic symptoms, TVUS studies have reported associations between adenomyosis and overactive bladder symptoms [90].

One frequently cited study suggested that adenomyosis is often an incidental finding rather than a condition diagnosed by a clinical presentation of symptoms. This interpretation was drawn from a lack of observed association between abnormal uterine bleeding and chronic pelvic pain symptoms and adenomyosis in 137 women who underwent hysterectomies. These women were part of a large, community-based study and were being followed through the menopausal transition; they constituted the subset who reported hysterectomies over nine years of follow-up. However, the eligibility criteria for entry into the longitudinal cohort included being aged 42-52 years, having an intact uterus, and, in the prior three months, having had at least one menstrual period without using reproductive hormones. Women with substantial symptoms managed by hysterectomy or hormonal medications were excluded from entering the study. This would however, decrease the sensitivity of the study to detect an association between abnormal uterine bleeding and chronic pelvic pain symptoms and adenomyosis [91].

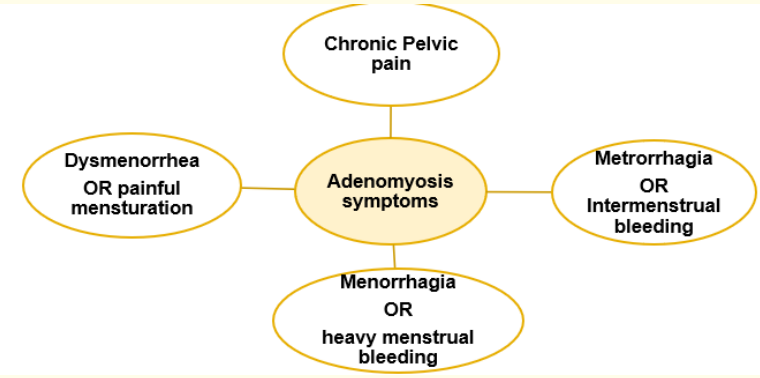

Figure 3: *Adenomyosis characterized by endometrial glands and stroma inside myometrium.*

Recent research indicates that adenomyosis has a detrimental impact on *in vitro* fertilization, pregnancy rates, and the likelihood of live births, while also raising the risk of miscarriage. Furthermore, adenomyosis increases the chances of obstetric complications, such as premature birth and early rupture of the amniotic sac. The fertility of individuals with adenomyosis may be disrupted through various mechanisms. These include abnormalities in the movement of gametes and embryos through the fallopian tubes, as well as disturbances in endometrial function and receptivity. Factors such as an enlarged uterus, anatomical distortions, and intramural adenomyomas can alter the shape of the uterine cavity, potentially hindering processes like sperm migration, embryo transfer, and implantation. Studies have suggested a link between spontaneous abortion and dysfunction of the junctional zone (JZ). Observations indicate that an enlarged JZ, particularly exceeding 7 mm, is associated with higher rates of implantation failure. Adenomyosis is also characterized by hyperactivity

of the myometrium, with changes observed at the cellular level including disruptions in calcium circulation leading to irregular muscle contractions. This results in dysfunctional uterine peristalsis, increased intrauterine pressure, and the development of hyperplastic myometrial tissue. Thickening of the junctional zone reflects the invasion of endometrial tissue into the myometrium, while altered myometrial contractility may impede sperm progression towards the fallopian tubes [88-91].

Diagnosis

The advancement of imaging diagnostic tools has revolutionized the non-invasive diagnosis of adenomyosis. Imaging plays a critical role in accurately diagnosing adenomyosis and tailoring appropriate management strategies, whether medical or surgical. Currently, most cases of Adenomyosis are treated medically without histological confirmation, making imaging techniques vital for diagnosis [92].

Presently, 2D (and occasionally 3D) transvaginal ultrasonography (TVUS) serves as the primary diagnostic tool for Adenomyosis. Ultrasound has become the frontline approach due to its accessibility, cost-effectiveness, examination capabilities, and high accuracy in detecting gynecological pathologies when performed by skilled sonographers [93]. Transvaginal ultrasonography, in particular, offers optimal visualization of the uterus and surrounding structures. Although transabdominal ultrasonography has limited value, it may be utilized when transvaginal access is impractical or in cases of significantly enlarged uteri. Typical ultrasound signs of Adenomyosis include a large uterus with regular external contour, asymmetrical myometrial walls, and a heterogeneous myometrium containing intramyometrial cysts. While these signs exhibit high specificity (>95%), their sensitivity is relatively low, around 30%. In contrast, TVUS shows higher sensitivity (65% to 81%) and specificity (65% to 100%) in detecting adenomyosis [94].

Various ultra-sonographic criteria are used for diagnosing adenomyosis, such as uterine enlargement, asymmetry of uterine wall thickness, heterogeneous myometrial areas, presence of myometrial cysts, and abnormalities in the endometrial-myometrial interface. Over time, advancements in TVUS techniques have significantly improved the accuracy of adenomyosis diagnosis, allowing for better detection of diffuse adenomyosis. Additionally, the presence of specific features like sub endometrial linear striations, echogenic nodules, or asymmetric myometrial thickness further enhance the diagnostic accuracy [95]. The study by Kepkep., *et al*. identified sub endometrial linear striations as the most specific sonographic feature (95.5% cases) with the highest positive predictive value (80.0%) for diagnosing adenomyosis [96]. Dueholm's review highlighted that transvaginal ultrasonography (TVUS) was highly dependent on the observer but could achieve adequate diagnostic accuracy when performed by experienced sonographers [97]. However, Gordts., *et al*. emphasized on the need for a common terminology and classification, highlighting the crucial role of the junctional zone (JZ) [98].

Colour flow Doppler imaging has further improved adenomyosis diagnosis by assessing vascular flow characteristics, thereby helping to differentiate Adenomyosis from uterine fibroids. Typically, "translesional flow" is observed in adenomyosis, while fibroids exhibit circular flow patterns [99]. Power Doppler ultrasound displays vessels perpendicular to the endometrial interface, providing further diagnostic insights, particularly in cases of posterior adenomyosis associated with deep infiltrating endometriosis (DIE) [100]. The introduction of 3D TVUS, high-frequency probes, and advanced modalities like volume contrast imaging (VCI) has enhanced the visibility of the JZ on ultrasound. 3D TVUS enables comprehensive assessment of the JZ, including its lateral and fundal aspects, offering clearer visualization of endometrial protrusions into the myometrium [101]. In recent years, the widespread use of imaging techniques has enabled adenomyosis diagnosis not only among women undergoing hysterectomy but also among those attending ultrasound gynecology units. Various studies have reported significant associations between adenomyosis and symptoms such as menstrual pain and heavy menstrual bleeding, emphasizing the clinical relevance of ultrasound-based diagnosis [102].

The Morphological Uterus Sonographic Assessment (MUSA) consensus, published in 2015, aimed to standardize the terminology for describing ultrasound images of normal and pathological myometrium. MUSA provides a comprehensive list of 2D and 3D ultrasound features associated with Adenomyosis, facilitating consistent reporting and enhancing diagnostic accuracy in both clinical and research

settings. The junctional zone (JZ) is normally observed as a dark sub endometrial edge visible on both 2D and 3D ultrasound (US). However, 3D US examination, with its multiplanar view of the uterus, including the coronal view, allows for a more detailed evaluation of the JZ. In cases of Adenomyosis, the JZ may appear irregular, interrupted, not visible, or not measurable [103].

The MUSA consensus established a standardized terminology for describing myometrial lesions, aiming to facilitate consistent reporting in both clinical practice and research. A more detailed reporting system for US findings of adenomyosis has been proposed, emphasizing the lesion's location (anterior, posterior, lateral left, lateral right, or fundal) and distinguishing between focal and diffuse types. Additionally, Adenomyosis involvement in the three uterine layers is classified into types 1, 2, and 3, based on the layer affected. The severity of adenomyosis can be classified based on the percentage of affected myometrium, ranging from mild (< 25%) to severe (> 50%). This classification system, proposed by expert sonographers, requires further validation in prospective studies to determine its accuracy and clinical relevance [104].

MRI serves as a second-line examination for diagnosing adenomyosis, with high sensitivity and specificity. Objective parameters for MRI diagnosis include thickening of the JZ, ratio of junctional zone maximum/total myometrium, and the difference between maximum and minimum JZ thickness. However, variations in JZ thickness due to factors like menstrual cycle phase, reproductive status, and medication use should be considered when interpreting MRI findings [105]. Common drawbacks in MRI diagnosis include variations in JZ thickness caused by transient uterine contractions, which can mimic adenomyosis features. Repeated MRI may be necessary to differentiate physiological conditions from adenomyosis accurately. Despite these challenges, MRI is considered valuable for diagnosing adenomyosis, particularly when combined with clinical and ultrasound findings [106].

Various classification systems for Adenomyosis have been proposed based on different criteria, including laparoscopic and histological findings, clinical presentation, and imaging features such as MRI and ultrasound. These classifications aim to provide a better understanding of adenomyosis and its subtypes, aiding in diagnosis and treatment planning. One classification system identified four types of adenomyosis: diffuse, sclerotic, nodular and cystic, which correlated with clinical presentation. Another classification categorized adenomyosis into diffuse, focal, polypoid adenomyomas, and special categories like adenomyomas of the endocervical type and retroperitoneal adenomyosis [107].

MRI-based classifications have identified three main types of adenomyosis: internal adenomyosis (focal, superficial, or diffuse), external adenomyosis (anterior or posterior), and adenomyomas, with subtypes based on lesion localization and content. Recently, a reporting and classifying system based on ultrasound findings has been proposed, but a shared classification system has not been universally adopted yet [108].

Other techniques like sonohysterography and hysteroscopy offer additional insights into adenomyosis, allowing visualization of endometrial signs indicative of the disease in addition to acting as an aid to rule out other diagnoses. Sonohysterography may demonstrate continuity between sub endometrial cystic spaces and the endometrial cavity, while hysteroscopy allows direct visualization of the uterine cavity [109]. While these techniques offer potential for improving diagnosis and understanding of adenomyosis, their applicability in everyday clinical practice and their effectiveness in guiding treatment decisions require further investigation. Additionally, considerations regarding cost, invasiveness, and patient distress must be taken into account [110].

Elastography is a technique that measures tissue stiffness by applying external tissue compression, similar to palpation, and analyzing the resulting strain or displacement within the tissue. The stiffness of tissues is then displayed in a range of false colors on elastography images. Elastography has been explored in the context of transvaginal ultrasound (TVUS) to differentiate between fibroids and adenomyosis. However, studies on elastography's ability to differentiate between these conditions have produced conflicting results regarding the stiffness of adenomyotic lesions. Some studies suggest that adenomyosis is associated with softer tissue characteristics, while others found lesion stiffness [111].

Despite advancements in imaging technology, there are still many uncertainties regarding the diagnosis and classification of adenomyosis. One challenge lies in correlating imaging features with the clinical presentation of adenomyosis. While imaging tools like MRI and TVUS can accurately detect adenomyosis, their ability to predict symptoms or outcomes is not yet fully understood. Additionally, the presence of symptoms alone may not always help in diagnosis, as a significant portion of patients with Adenomyosis are asymptomatic or may have overlapping symptoms with other gynecological conditions [112]. The existing classifications of adenomyosis propose different phenotypes based on various parameters such as affected area, localization, and pattern. However, there is a lack of consensus and uniformity in terminologies and definitions for these classifications. Key parameters for inclusion in a classification system could include the affected area within the myometrium, localization within the uterus, and the pattern and size of lesions. An ideal imaging technique should not only accurately diagnose Adenomyosis but also provide valuable information for treatment decision-making and outcome prediction [113].

Through collaborative initiatives, researchers and clinicians can work together to refine diagnostic criteria, validate imaging techniques, and establish evidence-based treatment guidelines. Furthermore, the development of minimally invasive procedures, such as radiofrequency and microwave ablation, as well as High-intensity Focused ultrasound (HiFu), are promising alternatives to traditional surgical and medical treatments. These techniques minimize the need for invasive procedures, reduce patient discomfort, and promote faster recovery times [114].

Diagnostic tools for Adenomyosis - Currently used
Transvaginal Ultrasonography (TVUS)
Colour flow Doppler Ultrasonography
Magnetic resonance imaging (MRI)
Histopathological findings
Sonohysterography
Hysteroscopy
Elastography
Diagnostic tools for Adenomyosis - Future prospects
High-intensity Focused ultrasound (HiFu)
Radiofrequency
Microwave ablation

Table 2: *Diagnostic tools for adenomyosis.*

Management of adenomyosis

Management of adenomyosis requires a multidisciplinary approach tailored to the patient's symptoms, desire for fertility, and overall health status. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to alleviate pain associated with Adenomyosis by reducing inflammation and prostaglandin production. NSAIDs are only for effective for symptomatic treatment and provide temporary relief. It does not address the underlying pathology of adenomyosis [115]. Hormonal therapies, such as oral contraceptives, progestins, and gonadotropin-releasing hormone (GnRH) agonists, aim to suppress menstrual bleeding and alleviate symptoms associated with Adenomyosis. GnRH agonists, in particular, induce a hypo estrogenic state, leading to symptom improvement in some patients. However, hormonal therapies are often associated with side effects such as weight gain, mood changes, and bone density loss [116]. Aromatase inhibitors block estrogen synthesis and have shown significant reduction in Adenomyosis-associated symptoms. However, their use is

limited by side effects such as hot flashes, joint pain, and potential adverse effects on bone health [117]. Uterine Artery Embolization (UAE) involves occluding the uterine arteries to reduce blood supply to adenomyotic lesions, thereby improving symptoms such as bleeding and pain. However, UAE is risky as it can cause complications such as infection, uterine perforation, and post-embolization syndrome [118].

Mirena, also known as the Levonorgestrel-releasing intrauterine device (IUD), is a commonly utilized treatment option for adenomyosis. This intrauterine device (IUD) continuously releases a low dose of the hormone Levonorgestrel directly into the uterine cavity, which can help alleviate symptoms associated with adenomyosis such as heavy menstrual bleeding and pelvic pain. By thinning the endometrial lining and reducing menstrual flow, Mirena can effectively manage adenomyosis-related symptoms in many individuals. Additionally, its localized delivery mechanism minimizes systemic hormonal effects, making it a preferred choice for those seeking non-oral hormonal therapies. Implanon and Depo-Provera (depot medroxyprogesterone acetate) injections are other hormonal treatment options commonly considered for adenomyosis management. Implanon is a subdermal contraceptive implant that steadily releases Etonogestrel, a progestin hormone, into the bloodstream over several years. Similarly, Depo-Provera injections administer medroxyprogesterone acetate, another synthetic progestin, at regular intervals to suppress ovulation and thin the uterine lining. These hormonal therapies can help alleviate adenomyosis symptoms by inducing amenorrhea (absence of menstruation) or reducing menstrual bleeding and pain. Mirena, while effective in managing adenomyosis symptoms, may also present certain complications and side effects. Some individuals may experience initial discomfort or cramping during or after insertion of the device, although this usually subsides over time. Additionally, irregular bleeding or spotting, particularly during the first few months after insertion, is common. In rare cases, Mirena may perforate the uterine wall during insertion or become partially expelled from the uterus, requiring removal or reinsertion. There is also a small risk of developing pelvic inflammatory disease (PID), although this risk is generally low, especially in individuals without preexisting infections. Implanon and Depo-Provera injections carry their own set of potential complications and side effects. Implanon users may experience irregular menstrual bleeding or changes in menstrual patterns. Some individuals may also report headaches, acne, breast tenderness, or mood changes as side effects of the hormonal implant. Similarly, Depo-Provera injections can lead to irregular menstrual bleeding, weight gain, mood changes, and decreased bone density with long-term use, particularly in individuals who receive injections over an extended period [118-120].

Prolactin (PRL) plays a significant role in the pathogenesis of adenomyosis, a condition characterized by the presence of endometrial tissue within the myometrium. Elevated PRL levels have been associated with increased proliferation and migration of endometrial stromal cells, contributing to the development of adenomyotic lesions. Animal studies have demonstrated that hyperprolactinemia can induce adenomyosis, and treatment with dopamine agonists like bromocriptine can suppress its development. In clinical settings, dopamine agonists such as bromocriptine and cabergoline, which inhibit PRL secretion, have shown efficacy in managing adenomyosis symptoms. Bromocriptine treatment has been observed to reduce menstrual bleeding and pain in women with adenomyosis. Additionally, it inhibits the proliferation and migration of endometrial stromal cells *in vitro*, suggesting a direct therapeutic effect on the pathological tissue. Cabergoline, another dopamine agonist, has also been associated with symptom resolution and radiological improvement in adenomyosis cases [119,120].

Adenomyomectomy involves surgical excision of adenomyotic lesions while preserving the uterus. This approach is suitable for patients who desire fertility preservation. However, adenomyomectomy may be challenging due to the diffuse nature of adenomyosis, and there is a risk of recurrence. Hysterectomy, or surgical removal of the uterus, remains the definitive treatment for adenomyosis, providing complete resolution of symptoms [121]. Variants such as subtotal hysterectomy (removal of the uterus while preserving the cervix) or laparoscopic hysterectomy may offer quicker recovery and reduce postoperative complications. However, hysterectomy is a major surgical procedure associated with risks such as bleeding, infection, and psychological impact [122].

For patients desiring fertility preservation, fertility-sparing options such as adenomyomectomy or hormonal therapies may be considered. Adenomyomectomy aims to remove adenomyotic lesions while preserving the uterus and fertility. However, recurrence rates

following adenomyomectomy can be significant, and the procedure may impact future fertility. Hysterectomy is the most effective surgical intervention for adenomyosis, providing complete resolution of symptoms. Adenomyomectomy and UAE offer symptom relief but may be associated with higher recurrence rates. However, Hysterectomy carries the highest risk of complications, including bleeding, infection, and injury to surrounding structures. Adenomyomectomy may be challenging due to the diffuse nature of adenomyosis and the risk of recurrence. UAE carries risks such as post-embolization syndrome and potential damage to surrounding organs. Conservative approaches such as UAE and adenomyomectomy may not be suitable for all patients, particularly those with extensive disease. Hysterectomy, while effective, is a definitive procedure that will not preserve fertility [121-123].

Complementary and alternative therapies, such as acupuncture, herbal supplements, and dietary modifications, are often used as adjunctive treatments for adenomyosis. While some patients may experience symptom improvement with these therapies, evidence supporting their efficacy is limited, and they should be used with caution in combination with conventional medical management [121]. Management of Adenomyosis requires a personalized approach tailored to the patient's symptoms, fertility desires, and overall health status. While medical management options only aim to alleviate symptoms, surgical interventions such as hysterectomy provide a definitive treatment for Adenomyosis. Fertility-sparing options such as adenomyomectomy may be considered for patients desiring future fertility, although recurrence rates can be significant. Ultimately, shared decision-making between patients and healthcare providers is essential to determine the most appropriate management strategy among all the options summarized in figure 5 for adenomyosis.

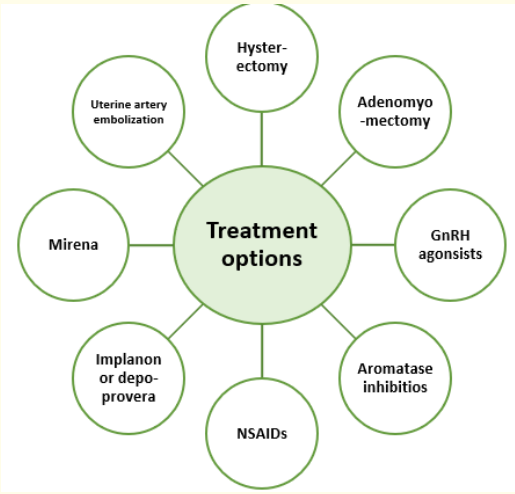

Figure 5: *Treatment options for adenomyosis.*

Future prospects

Adenomyosis presents a complex clinical challenge with diverse symptomatology and limited treatment options. There are several promising avenues for future research aimed at improving diagnostic accuracy and therapeutic outcomes. One key area of investigation is the identification of reliable biomarkers associated with Adenomyosis. Biomarkers could help in early diagnosis and monitoring disease progression. Potential biomarkers are circulating hormones, inflammatory markers, and microRNAs associated with adenomyosis [122].

Advancements in molecular imaging techniques, such as positron emission tomography (PET) have a promising future for non-invasive detection of adenomyotic lesions. Integration of artificial intelligence (AI) and machine learning algorithms into imaging modalities

could enhance diagnostic accuracy and efficiency in identifying adenomyotic lesions. AI-based systems may analyze imaging data to differentiate adenomyosis from other uterine pathologies and predict treatment response [123].

Research into novel therapeutic strategies for adenomyosis could lead to the development of pharmacological agents aimed at targeting disease-specific pathways. These may include inhibitors of angiogenesis, inflammation, or hormone signaling pathways involved in the pathogenesis of adenomyosis. Considering the immune dysregulation in adenomyosis, immunomodulatory therapies could be used for symptom management. Immunomodulators targeting specific immune cell subsets or inflammatory mediators could reduce disease-associated inflammation and tissue remodeling [124].

High-intensity focused ultrasound (HIFU) therapy offers a non-invasive approach for targeted ablation of adenomyotic lesions. Further research is needed to optimize HIFU treatment parameters, assess long-term efficacy, and evaluate its safety profile in larger patient cohorts. Development of novel drug delivery systems, such as localized drug-eluting devices or nanoparticles, may allow targeted delivery of pharmacological agents to adenomyotic lesions while minimizing systemic side effects. Drug-eluting intrauterine devices or biocompatible implants could provide sustained release of therapeutic agents directly to the affected tissue [125].

Future research should prioritize patient-centered outcomes to improve quality of life, symptom burden, and treatment satisfaction. Longitudinal studies are needed to assess the disease progression over time, and factors influencing treatment outcomes. Prospective cohort studies with long-term follow-up can provide valuable insights into the efficacy of various treatment modalities. Collaboration between researchers and clinicians is essential to progress towards improved outcomes for patients with Adenomyosis [126,127].

The emerging evidence linking prolactin to the pathogenesis of adenomyosis opens critical avenues for research that must now shift from observational associations to mechanistic clarity. Studies should focus on how prolactin alters endometrial-myometrial interface biology particularly its role in promoting cellular invasiveness, angiogenesis, and local inflammation. There is a clear clinical need to investigate dopamine agonists such as cabergoline and bromocriptine in rigorously designed trials, not just for symptom control but as disease-modifying agents. Additionally, exploring prolactin as a biomarker for disease progression or treatment response could refine diagnostic precision. Moving forward, the field must embrace a more targeted, hormone-focused therapeutic strategy, positioning prolactin not as a peripheral player, but as a central therapeutic axis in adenomyosis management [128].

Conclusion

In conclusion, Adenomyosis is a complicated gynecological condition characterized by the ectopic presence of endometrial tissue within the myometrium. Despite significant advancements in our understanding of its pathogenesis, clinical presentation, diagnosis, and management, adenomyosis remains a complex and challenging disorder to diagnose and treat effectively.

The pathogenesis of adenomyosis involves a combination of factors that contribute to the invagination of endometrial tissue into the myometrium. This unusual tissue growth results in a spectrum of clinical manifestations, ranging from asymptomatic cases to severe pelvic pain, abnormal uterine bleeding, and reproductive dysfunction [65,66]. The variety in clinical presentation emphasizes the importance of individualized diagnostic and therapeutic approaches tailored to each patient's needs. Diagnostic modalities for adenomyosis have evolved over the years, with advances in imaging techniques such as transvaginal ultrasound, MRI, and elastography offering non-invasive methods for detecting and characterizing adenomyotic lesions. However, challenges include standardizing diagnostic criteria and distinguishing adenomyosis from other uterine pathologies, highlighting the need for further research in this area [93,94].

Management of adenomyosis includes medical, surgical, and minimally invasive interventions aimed at alleviating symptoms, preserving fertility, and improving quality of life. Medical therapies such as analgesics, hormonal agents, and novel approaches like

aromatase inhibitors offer symptomatic relief but may be limited by side effects and long-term efficacy. Surgical interventions including adenomyomectomy and hysterectomy remain definitive treatment options but involves risks and implications for future fertility [118-120].

Future research in adenomyosis should focus on clarifying the underlying mechanisms for disease progression, identifying biomarkers for early detection, and developing therapies that target the specific pathological pathways involved in adenomyosis [122]. Additionally, efforts to standardize diagnostic criteria and improve imaging modalities will be crucial in enhancing patient outcomes. By advancing approaches to diagnosis and treatment, the complexities of adenomyosis can be effectively cured and the lives of patients living with this challenging condition can be significantly improved.

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