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REVIEW

The First Lugano Workshop on the role of adenomyosis in ART

BIOGRAPHY

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KEY MESSAGE

Adenomyosis may impact the outcomes of IVF, particularly miscarriage; however, more studies excluding embryo factors are warranted. Freeze-all strategies with protracted hormonal suppressive treatments reducing hyperoestrogenism and high-dose progesterone seem a good choice before embryo transfer in women with adenomyosis; however, the evidence is still weak. The pathogenesis of the disease should be clarified further.

ABSTRACT

Adenomyosis is an important clinical condition with uncertain prevalence, and clinical focus on adenomyosis in patients undergoing assisted reproductive technology (ART) has increased during recent years. Recognizing the limited clinical knowledge on the impact of adenomyosis on ART outcomes, the First Lugano Adenomyosis Workshop was a symposium involving experts in the field of adenomyosis, covering basic research, imaging, surgery and infertility to highlight current advances and future research areas over a wide range of topics related to adenomyosis. Adenomyosis is characterized by altered oestrogen and progesterone signalling pathways. Although the criteria of the Morphological Uterus Sonographic Assessment (MUSA) Consortium apply to patients with infertility, the presence of direct signs and localization in the different myometrial

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KEY WORDS

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layers, particularly the inner myometrium, need more focus. In addition to the MUSA criteria, clinical symptoms and the magnitude of uterine enlargement should also be considered. Whilst pre-treatment with gonadotrophin-releasing hormone agonist with or without an aromatase inhibitor in frozen embryo transfer cycles seems promising, many issues related to therapy remain unanswered. During the Workshop, therapeutic progress over the past decades as well as novel insights were presented and discussed. The role of this opinion paper is to stimulate discussion and spark further interest in adenomyosis and the role of adenomyosis in infertility.

INTRODUCTION

In Spring 2023, Drs Cozzolino and Humaidan met to discuss the optimal clinical handling of patients with adenomyosis undergoing IVF, as both had a specific interest in this growing group of patients. Recognizing that the focus on patients with adenomyosis from an infertility perspective was rather scanty, a decision was made to invite a group of opinion leaders from the USA and Europe within basic science, imaging, surgery and reproductive medicine for a 1.5-day workshop in Lugano (Switzerland). This review summarizes the content and conclusions of the First Lugano Adenomyosis Workshop.

EPIDEMIOLOGY

Adenomyosis is a classical diagnosis made by pathologists on a uterine biopsy after a hysterectomy. The typical pathological description is 'benign invasion of the endometrium, producing a diffusely enlarged uterus, which microscopically exhibits ectopic, non-neoplastic, endometrial glands and stroma surrounded by hypertrophic and hyperplastic myometrium' (*EMGE, 1962*). Three different phenotypes are described: diffuse, focal (adenomyoma or cystic) and polypoid. These phenotypes have been described and classified following the introduction of magnetic resonance imaging (MRI) and transvaginal ultrasound (TVUS) (*Bazot and Darai, 2018*; *Harmsen et al., 2022*). At the same time, according to the classification of the International Federation of Gynecology and Obstetrics, adenomyosis is among the structural causes of abnormal uterine bleeding (AUB) (*Munro et al., 2011*)

The lack of a common criterion explains the huge difference in prevalence of adenomyosis reported in the literature (*Upson and Missmer, 2020*). The epidemiology of adenomyosis is difficult to define, as the diagnosis classically derives from the prevalence of adenomyosis seen after hysterectomy, ranging between 10% and 58% among different pathologists.

According to the symptoms (AUB, dysmenorrhoea and infertility), the prevalence of adenomyosis is 20–30% (*Upson and Missmer, 2020*), increasing to 25–35% when imaging is associated with symptoms. Thus, in future, only studies using common diagnostic criteria will allow the real epidemiology of adenomyosis to be defined.

Regarding risk factors, these have been modified over the last two decades. Initially, adenomyosis was described as a perimenopausal disorder, related to multiparity or prior uterine surgery, but nowadays it is also recognized in adolescents and young women during reproductive life (*Chapron et al., 2020a*). Age at menarche and heavy menstrual bleeding (HMB) are risk factors for adenomyosis, supporting the role of ovarian sex steroid hormones in the pathogenesis of the disease. Dysmenorrhoea, dyspareunia and AUB are the most typical clinical manifestations, affecting the quality of life of the patient. Adenomyosis is frequently discovered in asymptomatic patients during infertility work-up before assisted reproductive technology (ART) treatment, as well as in patients with recurrent pregnancy loss (RPL) (*ESHRE Guideline Group on RPL et al., 2023*).

DEFINING ADENOMYOSIS

Pathogenesis and basic science

Adenomyosis is an oestrogen-dependent gynaecological disorder characterized by the presence of endometrial epithelial cells and stromal fibroblasts within the myometrium (*Zhai et al., 2020*). Despite many of the questions regarding the pathogenesis of adenomyosis remaining unanswered, there are compelling data to support several overarching theories. The most recognized theories include: (i) invasion of the endometrial basalis into the myometrium; (ii) repeated microtrauma of the endometrial–myometrial interface; (iii) de-novo metaplasia of adult stem cells in the myometrium; and (iv) invasion of endometrial cells from retrograde menstrual effluent through the uterine serosa and into the myometrium (*Zhai et al., 2020*). Each of these theories recognizes the influence of a combination of genetic, epigenetic, hormonal, environmental and mechanical factors. The theory of invagination is one of the most widely accepted hypotheses on the pathogenesis of adenomyosis. According to this theory, adenomyosis arises from the invasion of altered endometrial cells into the myometrium through defects in the junctional zone. This theory was supported by evidence that eutopic endometrial stromal fibroblasts from women with adenomyosis have enhanced capacity to invade the myometrium (*Mehasseb et al., 2010*), as well as enhanced endometrial cell proliferation and survival (*Li et al., 2019*). Invagination of the endometrium, cell migration, and growth of ectopic lesions may also relate to direct dysregulation of the extracellular matrix (*Herndon et al., 2016*). Another theory focuses on the presence of hypercontraction and peristalsis of the myometrium due to microtrauma of the endometrial–myometrial interface, which causes mechanical stress on the myometrial fibres at the endometrial–myometrial junction (*Leyendecker et al., 2009*). This process induces local oestrogen production through the cyclo-oxygenase-2 and prostaglandin E2 pathways, leading to angiogenesis and repair. In addition, it has been demonstrated that endometrial cells from retrograde menstrual bleeding can invade the uterine serosa and the myometrium; this theory may explain the mechanism for the pathogenesis of focal adenomyosis associated with deep infiltrating endometriosis (*Chapron et al., 2017a*).

In parallel to recent advances in the diagnosis of adenomyosis, the pathophysiology of adenomyosis has also become better understood due to the emergence of next-generation-sequencing-related technologies (*Bulun et al., 2021*; *Chapron et al., 2020b*; *Inoue et al., 2019*; *Yildiz et al., 2023*). A ground-breaking study, employing deep sequencing of DNA on hundreds of multiregional biopsies of many uterine

specimens with adenomyosis, tediously mapped identical tumour-driver epithelial mutations in eutopic endometrium to adjacent adenomyotic tissue (*Inoue et al., 2019*). This study concluded that the epithelial cells of adenomyosis originate from the adjacent eutopic endometrium (*Inoue et al., 2019*). A follow-up single-cell RNA sequencing study suggested that the stromal cell component of adenomyosis also originated from the eutopic endometrium (*Bulun et al., 2021*). These two studies supported the long-held view that adenomyotic tissue originates from adjacent basal endometrium via its entrapment in the myometrium (*Leyendecker et al., 2006*). The menstruation process itself may increase the risk of entrapment of fragments of the basal layer within the myometrium.

Repetitive menstrual episodes imply reiterative tissue hypoxia, necrosis, myometrial contractions, angiogenesis and regenerative processes (*Bulun et al., 2021*; *Vercellini et al., 2024b*). These events may disrupt the endometrial–myometrial junction, favouring intramyometrial invagination of basal endometrial fragments, characterized by somatic mutations, conferring specific advantages for the development of adenomyosis (*Bulun et al., 2021*). In this context, it should be taken into consideration that, in comparison with pre-industrial times, more women now experience repetitive ovulatory menstruation, prolonged oestrogen exposure, and the absence of hypo-oestrogenic phases (*Vercellini et al., 2024b*). Thus, adenomyosis may be a disorder initiated by repetitive ovulatory menstruation in susceptible individuals, promoted by a mitogenic, pro-inflammatory and hyper-oestrogenic milieu.

Regarding recently discovered epithelial mutations, both the cancer driver PIK3CA and KRAS mutations were found in histologically normal eutopic endometrium in subjects with or without adenomyosis, whereas the epithelial cells and adjacent endometrium in women with adenomyosis almost exclusively displayed KRAS mutations (*Inoue et al., 2019*). KRAS was also the most recurrently mutated gene in epithelial cells of endometriotic lesions (*Bulun et al., 2021*). Oligoclones of endometrial glandular epithelial cells carrying these somatic mutations and attached stromal cells may thus travel retrogradely to peritoneal surfaces to cause endometriosis, or be entrapped in the myometrium, giving rise to adenomyosis (*Bulun et al., 2021*, *2023a*). Shared KRAS and non-KRAS mutations were found in cases with co-occurring adenomyosis and endometriosis (*Inoue et al., 2019*); however, there is no published evidence that a KRAS mutation *per se* can initiate adenomyosis or endometriosis (*Habiba et al., 2023*).

Dependence on ovarian steroids and ovulatory cycles for disease development has been shown in adenomyosis. In this context, common patterns of aberrant gene expression have been reported in adenomyosis, including pathways that favour increased local oestrogen biosynthesis, an oestrogen receptor-beta (ESR2)-driven inflammatory process, and progesterone resistance due to decreased expression of progesterone receptors (*Bulun et al., 2021*).

DIAGNOSING ADENOMYOSIS

Imaging

Historically, MRI has been used as a non-invasive diagnostic tool for adenomyosis. However, over the last decades, TVUS has become the first-line imaging tool in most centres, particularly infertility clinics. MRI and TVUS have demonstrated the importance of 'direct' signs of adenomyosis. Direct signs reflect the presence of ectopic endometrial tissue in the myometrium (e.g. myometrial echogenic islands, subendometrial hyperechogenic buds or myometrial cysts with an echogenic rim on TVUS; bright spots on MRI), whereas indirect signs are the consequence of the extra ectopic tissue within the myometrium (e.g. globular or asymmetrical myometrial enlargement, and fan-shaped shadowing). The Morphological Uterus Sonographic Assessment (MUSA) Consortium described the direct and indirect signs of adenomyosis (*Harmsen et al., 2023a*,*b*; *Van den Bosch et al., 2015*, *2019*), and while it is generally accepted that direct signs are indispensable to diagnose adenomyosis, the Lugano Workshop Group highlights the need for simple diagnostic guidelines to be applicable in daily clinical practice to describe the type and extension of the disease in the myometrium. The presence of direct signs (i.e. intramyometrial cystic areas and hyperechoic islands or buds) and localization in the different myometrial layers, particularly the inner myometrium or junctional zone, should be the focus in infertile patients. Also, the type of adenomyosis (i.e. diffuse, focal or combined) is important, as the extent of disease and uterine volume are considered essential when evaluating the true impact of adenomyosis on fertility.

Moreover, the importance of the absence or presence of symptoms associated with adenomyosis (i.e. dysmenorrhoea, dyspareunia and/or HMB) should be explored in fertility patients. Fibroids should be differentiated from adenomyosis, but could occur concomitantly. Moreover, the association between adenomyosis and different types of pelvic endometriosis (e.g. endometriomas or deep endometriosis of the posterior, anterior or lateral compartment) should also be better defined and compared. Ultrasonography and MRI show similar diagnostic accuracy in evaluating the presence of adenomyosis, whereas differences are seen in the description and classification of the type and extension of the disease inside the uterus. To simplify the diagnosis, it is suggested that both imaging modalities should describe the disease, as shown in **TABLE 1**. Qualified training in gynaecological ultrasonography for gynaecologists and sonographers working in fertility centres will enable better detection of the different phenotypes of adenomyosis. This may prove key for a better understanding of the disease, and hence optimization of fertility treatment.

New diagnostic molecular approaches in adenomyosis

Classically, adenomyosis has been diagnosed by clinical symptoms and imaging studies, with their limitations. Understanding the underlying molecular mechanisms involved in the pathogenesis of adenomyosis is essential to manage adenomyosis-related infertility. Advances in molecular diagnostics may open new avenues for more precise methodologies that could allow earlier detection. Currently, there is a strong interest in the study of genetic and molecular markers associated with adenomyosis, and the dysregulated mechanisms involved in decidualization, endometrial receptivity and embryo implantation, and new tools are being developed as diagnostic tests.

A better understanding of how inflammation or hormonal signalling may be disrupted in women with the disease, or even altered gene expression profiles that could lead to unique molecular markers,

TABLE 1 SIMPLIFIED AND SCHEMATIC DIAGNOSTIC REPORTING OF ADENOMYOSIS

Junctional zone	Middle/outer myometrium	Diffuse[a]	Focal[b]	UTERINE VOLUME (cc)
DIRECT SIGNS[c]				Intramural fibroids (FIGO 3–5) >3 cm (*n*)
Intramyometrial cystic areas				SYMPTOMS
Intramyometrial hyperechoic island				Dysmenorrhoea (VAS)
ENDOMETRISIS				Dyspareunia (VAS)
Endometrioma				Dysuria (VAS)
Posterior DE				Dyschezia or other bowel symptoms (VAS)
Anterior DE				Chronic pelvic pain (VAS)
Lateral DE				Heavy menstrual bleeding (PBAC)

[a] Direct signs dispersed over the myometrium.

[b] Direct signs surrounded by normal myometrium.

[c] On magnetic resonance imaging, high-intensity foci (≤3 mm) within the myometrium.

DE, deep endometriotic lesion; PBAC, pictorial blood loss assessment chart; VAS, visual analogue scale; FIGO, International Federation of Gynecology and Obstetrics.

will most certainly prove helpful when distinguishing adenomyosis from other uterine conditions. A global interest in identifying a panel of biomarkers that may help diagnose adenomyosis is on the minds of many researchers.

Current research with precise technology, such as single-cell RNA sequencing, is aiming to decipher the transcriptional alterations in the endometrium, adenomyotic lesions and the endometrial–myometrial junction. To date, aberrant signalling cascades have been described, including pleiotrophin, tumour-necrosis-factor-related weak inducer of apoptosis, and wingless/integrated pathways, among others. Being able to identify dysfunctional signalling could be critical to developing diagnostic strategies.

Moreover, the possibility of generating and differentiating endometrial organoids facilitates research in this field. Organoids derived from patients with adenomyosis are helpful tools to overcome the difficulty and barriers to obtaining research samples, and this model allows the identification of dysregulated genes and pathways in the endometrium that may be responsible for the implantation failures and miscarriages experienced by women with adenomyosis (*Juarez-Barber et al., 2023*).

Similar to other inflammatory diseases, such as endometriosis, where miRNA are being investigated as early diagnostic markers (NCT05244668), it would be interesting to investigate a non-invasive diagnostic approach for women with adenomyosis. It may be necessary to rewind and redefine the disease by first understanding its pathogenesis, and subsequently – based on those findings – suggest new diagnostic approaches, even prior to the disease being visible on ultrasound.

RELATIONSHIP BETWEEN ENDOMETRIOSIS AND ADENOMYOSIS

Adenomyosis and endometriosis are two benign gynaecological pathologies that frequently co-exist (*Chapron et al., 2019*). The prevalence of adenomyosis associated with endometriosis varies between studies, but some authors have reported that the prevalence of adenomyosis in women with endometriosis is between 80% and 90% (*Eisenberg et al., 2017*). Other studies have reported adenomyosis in less than half of patients with endometriosis (*Naftalin et al., 2012*), or no relationship between adenomyosis and endometriosis (*Vavilis et al., 1997*). Interestingly, the association between these two pathologies appears to depend on the phenotype (*Chapron et al., 2017b*; *Kishi et al., 2012*).

Adenomyosis, like endometriosis, is a heterogeneous condition, presenting in two main forms: diffuse adenomyosis of the inner myometrium, and focal adenomyosis of the outer myometrium (*Chapron et al., 2017b*; *Van den Bosch et al., 2019*). A previous study in women with histologically proven endometriosis found that diffuse adenomyosis occurred in one-third of the patients, irrespective of whether they were endometriotic patients or controls, and was not associated with the phenotype of endometriosis (*Chapron et al., 2017b*). Several teams have shown that focal adenomyosis is observed in up to 66% of cases in women with deep infiltrating endometriosis (*Chapron et al., 2017b*; *Kishi et al., 2012*).

While endometriosis and its related symptoms do not appear to play a major negative role in embryo implantation (*Maignien et al., 2023*, *2024*; *Paffoni et al., 2024*), recent evidence suggests an alteration in reproductive outcomes in cases associated with adenomyosis (*Bourdon et al., 2022a*; *Sharma et al., 2019*; *Thalluri and Tremellen, 2012*). Furthermore, the association of adenomyosis and endometriosis significantly impacts the therapeutic management outcomes of endometriosis. It has been shown that, following radical surgical treatment of deep colorectal endometriosis, the presence of pre-operative adenomyosis leads to decreased postoperative conception rates compared with women without adenomyosis (*Ballester et al., 2012*). Even in the specific context of severe endometriosis and repeated IVF failure, the effectiveness of complete laparoscopic surgery, including the excision of all endometriotic lesions, is diminished by the presence of pre-operative uterine adenomyosis (*Soriano et al., 2016*). Additionally, following surgical excision of endometriosis, chronic pelvic pain is significantly more likely to persist in the presence of pre-operative adenomyosis (*Parker et al., 2006*).

These data suggest that adenomyosis is frequently associated with endometriosis, and may contribute to both chronic pelvic pain and reduced fertility in women with endometriosis. Given the substantial

heterogeneity of adenomyotic lesions, future studies should characterize the clinical impact of the different phenotypes accurately to better personalize therapeutic strategies.

SYMPTOMATIC VERSUS ASYMPTOMATIC ADENOMYOSIS

As mentioned above, adenomyosis is currently diagnosed by TVUS and MRI. Typically, TVUS and MRI are undertaken in the case of uterine symptoms evocative of adenomyosis, such as AUB and/or dysmenorrhoea. Adenomyosis will also typically be diagnosed by imaging prescribed due to suspected endometriosis and/or performed routinely because of repeated ART failure. In the latter case, adenomyosis is believed to be asymptomatic. The imaging-based diagnoses encompass, therefore, cases with markedly different clinical patterns and findings. Schematically, this includes women with an enlarged uterus and clinical symptoms of adenomyosis, and women with a normal-sized uterus without subjective complaints.

There is little doubt that women with a markedly enlarged uterus and who complain of uterine cramping and menstrual disorders experience reduced fertility, and notably decreased receptivity to embryo implantation (*Bourdon et al., 2022b*).

Patients with symptomatic adenomyosis may experience lower pregnancy rates when undergoing IVF treatment compared with women with asymptomatic adenomyosis, as reported in a recent meta-analysis (*Wang et al., 2023*). This is because the symptoms of adenomyosis, such as HMB, pelvic pain and dysmenorrhoea, often indicate a more severe condition that has a negative impact on fertility. Hence, uterine measurement by ultrasound and careful reviewing of clinical symptoms are crucial. Increased menstrual flow, the presence of clots and uterine cramping are amongst the most important menstrual symptoms to consider.

Women with asymptomatic adenomyosis and a normal-sized uterus do not seem to have a worse ART outcome, contrary to findings reported in women with an enlarged uterus (*Wang et al., 2023*). Additionally, symptomatic adenomyosis may be associated with a higher level of inflammation and hormonal imbalances that can have a negative impact on embryo implantation and reproductive outcomes, and medical treatments for endometriosis and/or adenomyosis share the property of suppressing ovarian function (*Sokteang et al., 2024*). Taken together, uterine size and subjective symptoms of adenomyosis are important, as they impact ART outcomes. However, most studies reporting on adenomyosis in patients undergoing ART treatment fail to indicate uterine size and the presence or absence of symptoms. As all concur to indicate that symptomatic adenomyosis alters endometrial receptivity, it is unfortunate that the impact of symptomatic and asymptomatic adenomyosis on endometrial receptivity has not been better investigated. Hence, it is suggested that future studies in adenomyosis should focus specifically on the two clinical manifestations — symptomatic and asymptomatic adenomyosis — to explore the impact in natural conception as well as in ART.

TREATMENT OF ADENOMYOSIS

Medical treatment

Medical management of adenomyosis poses a substantial challenge due to the limited evidence available. The existing literature is scarce, with only one international guideline, the SOGC Clinical Practice Guideline (*Dason et al., 2023*), providing recommendations. Since 2001, only 15 medical approaches have been assessed for adenomyosis, with a total of eight randomized controlled trials (RCT) targeting this condition specifically. The overall quality of evidence is poor, and there is considerable variation in the reporting of endpoints, hindering effective trial comparisons.

Various medical treatments have been studied for adenomyosis, including non-steroidal anti-inflammatory drugs, tranexamic acid, progestins [e.g. levonorgestrel intrauterine system (LNG-IUS) and dienogest], gonadotrophin-releasing hormone (GnRH) agonists and antagonists, aromatase inhibitors, and vaginal bromocriptine (*Etrusco et al., 2023*; *Vannuccini et al., 2018*). Of all treatments, LNG-IUS and dienogest are the best-studied medications overall for symptomatic adenomyosis.

The LNG-IUS has been shown to reduce pain scores, bleeding and uterine volume [in comparison with hysterectomy or combined oral contraceptives (COC)] in two RCT (each ≤100 participants), with some longitudinal studies demonstrating sustained symptom control (*Abbas et al., 2020*; *Shaaban et al., 2015*; *Steward et al., 2011*). Dienogest (in comparison with placebo or COC; two RCT <100 participants) has shown promise in managing the pain of adenomyosis with sustained benefit (*Hassanin et al., 2021*; *Ono et al., 2021*; *Osuga et al., 2017*).

In terms of reproductive outcomes, medical management has shown some positive impact on ongoing pregnancy rates, especially when used as pre-treatment before ART treatment. Thus, a retrospective cohort study (n = 358) reported a significantly higher ongoing pregnancy rate (41.8% versus 29.5%) in women with adenomyosis pre-treated with LNG-IUS for 3 months before frozen embryo transfer (*Liang et al., 2019*). Retrospective studies have also suggested that GnRH agonist pre-treatment may be beneficial in improving the pregnancy rate and decreasing the miscarriage rate in ART patients with adenomyosis (*Cozzolino et al., 2022*; *Lan et al., 2021*; *Niu et al., 2013*; *Park et al., 2016*; *Stanekova et al., 2018*; *Tremellen and Russell, 2011*; *Wu et al., 2022*).

Importantly, the fact that observational studies report a link between adenomyosis and reduced IVF success does not prove causation. Interventional studies involving specific hormonal treatment of adenomyosis (GnRH agonist treatment) provide better proof of causation.

A search on clinicaltrials.gov (1 April 2024) identified four trials, active and recruiting, investigating different medical treatment approaches to potentially improve reproductive outcomes (NCT03946722, NCT04356664, NCT03421639, NCT06239376). The possible benefit of aromatase inhibitors in the treatment of adenomyosis and for the IVF setting needs further exploration (*Cozzolino et al., 2023*).

The lack of large-scale RCT and standardization in outcome measures of adenomyosis treatment still pose substantial challenges when determining the most effective medical approach for the condition. However, ongoing research, as listed in clinicaltrials.gov, holds promise for further elucidating the optimal medical management strategies of adenomyosis to hopefully improve ART results.

Surgical treatment

When to refer?

Evidence-based recommendations for surgery to improve reproductive outcomes among patients with adenomyosis are difficult to establish. This is due to heterogeneity between the adenomyosis phenotypes and the procedures themselves. Prior meta-analyses and systematic reviews suggest either modest or lack of benefit to undergoing surgery, perhaps with a greater advantage among younger patients with focal adenomyosis (*Dueholm, 2017*; *Jiang et al., 2023*; *Tan et al., 2018*).

In fertility practice, surgical intervention is usually limited to patients with focal adenomyosis, involving the endometrial cavity directly, and who failed medical management. Such patients include those who continue to harbour adenomyomas, resulting in a mass effect on the intracavitary space; or those with adenomyotic cysts that communicate with the cavity, leaking potentially pro-inflammatory material akin to hydrosalpinx. The latter group of patients often have intracavitary fluid, recurrent polyps, and synechiae despite recent surgical management, and hysteroscopic excision of the cysts shares similarities with performing hysteroscopic lysis of adhesions. The approach to non-cystic or adenomyomatous disease impacting the cavity involves conservative hysteroscopic resection of the protruding aspect of the adenomyoma. Rarely, a focal adenomyoma found at the time of abdominal myomectomy may be debulked, with careful consideration of maintaining adequate myometrium for future pregnancies.

The overall conservative approach to surgical management stems from both the lack of clear data in support of surgery among patients actively pursuing pregnancy, as well as the risk of profound complications during pregnancy following invasive procedures. Thus, the uterine rupture rate has been reported to be between 2.8% and 12% following abdominal adenomyomectomy (*Osada, 2018*), and increased risk of rupture was seen among patients undergoing debulking of diffuse adenomyosis (*Tan et al., 2018*).

High-intensity focused ultrasound (HIFU) is a non-invasive local thermal ablation technique which has been used in the treatment of both focal and diffuse adenomyosis. Several case studies have demonstrated that HIFU presents a low rate of minor and/or major complications and, at the same time, a long period of symptom relief (*Zhang et al., 2017*).

Women with adenomyosis treated with HIFU have shown high conception and live birth rates; as such, HIFU seems to be a promising treatment option. However, efficacy, safety, cost-effectiveness and reproductive outcomes must be evaluated by RCT. Taken together, current data suggest a potential benefit of HIFU in the treatment of adenomyosis-related symptoms; however, the lack of data comparing HIFU with other treatment regimens at present hampers generalization (*Marques et al., 2020*).

IMPACT OF ADENOMYOSIS ON ART OUTCOMES

Although a clear consensus regarding the negative effect of adenomyosis on ART outcomes has not been reached, three meta-analyses to date have concluded that adenomyosis reduces the pregnancy rate and increases the miscarriage rate in ART (*Cozzolino et al., 2024b*). Unfortunately, several of the studies included in the meta-analyses were biased because the diagnosis of adenomyosis was not set according to the MUSA criteria (*Van den Bosch et al., 2019*).

Recently, a prospective cohort study explored the reproductive outcomes of 99 patients with adenomyosis compared with 549 patients without adenomyosis undergoing preimplantation genetic testing for aneuploidy and subsequent frozen/thaw embryo transfer (HRT-FET). In this study, no difference in the live birth rate was seen between patients with and without adenomyosis (*Neal et al., 2020*).

Importantly, most patients in the study fulfilled only one MUSA criterion, whereas 17 patients met two criteria; the latter group experienced a slight, but not significant, decrease in live birth rate. Thus, women who meet a single MUSA criterion may present a less severe phenotype of adenomyosis compared with women meeting more MUSA criteria.

Another prospective cohort study, this time in oocyte recipients, suggested that adenomyosis did not hamper implantation significantly; however, the presence of adenomyosis increased the early miscarriage rate, resulting in a live birth rate of 36.8% in the patients with adenomyosis ($n = 114$) compared with 43.9% in the patients without adenomyosis ($n = 114$) (*Cozzolino et al., 2024b*). Although the difference was 7% in favour of non-adenomyosis, the difference did not reach significance with the present sample size. In support of these findings, a recent retrospective cohort study in HRT-FET including a total of 3503 patients undergoing their first blastocyst transfer, of whom 140 were diagnosed with adenomyosis, showed that adenomyosis significantly decreased the clinical pregnancy rate [adjusted OR (aOR) 0.62, 95% CI 0.39–0.98; $P = 0.040$] and live birth rate (aOR 0.46, 95% CI 0.27–0.75; $P = 0.003$), and significantly increased the miscarriage rate (aOR 2.13, 95% CI 0.98–4.37; $P = 0.045$) (*Sachs-Guedj et al., 2023*).

Thus, although results from RCT have not been published to date, a growing body of scientific evidence suggests that the presence of adenomyosis has a negative impact on the outcome of ART. Importantly, junctional zone involvement and severe adenomyosis according to the MUSA criteria appear to be important risk factors for miscarriage, highlighting the importance of an accurate ultrasound diagnosis and classification (*Cozzolino et al., 2024b*).

Although mid-luteal serum progesterone cut-off levels in HRT-FET have been explored thoroughly in patients without adenomyosis, the optimal mid-luteal serum progesterone concentration remains unexplored in patients with adenomyosis. Interestingly, a recent cohort study in a total of 179 patients with endometriosis suggested an optimal serum progesterone cut-off concentration for live birth of 118 nmol/l (37.1 ng/ml) in HRT-FET – a level nearly four times higher compared with patients without endometriosis (10 ng/ml) (*Alsbjerg et al., 2023*), in support of progesterone resistance in patients with endometriosis. Patients below the suggested cut-off [≥118 nmol/l (37.2 ng/ml)] had a live birth rate of 34% per transfer compared with 54% in patients above this cut-off. The data of this uncontrolled study apply principally to the endometriosis setting, and endometriosis and adenomyosis are defined as 'siblings' in their pathophysiology. Although the importance of progesterone to sustain pregnancy in women with adenomyosis is undoubted, the cut-off in HRT-FET

suggested by *Alsbjerg et al. (2023)* needs to be corroborated in future studies. Moreover, a recent retrospective study reported no difference in serum progesterone cut-off concentrations in terms of live birth rates in women with and without endometriosis (cut-off 13.6 ± 4.3 ng/ml versus 13.2 ± 4.4 ng/ml, respectively) (*Bourdon et al., 2024*). However, important differences exist between the two studies in terms of luteal phase support; thus, *Alsbjerg et al. (2023)* used vaginal micronized progesterone (90 mg bid) as well as i.m. progesterone 50 mg once daily for luteal phase support, whereas *Bourdon et al. (2024)* used vaginal micronized progesterone alone, which resulted in a luteal mean serum progesterone concentration nearly three times higher in the study by *Alsbjerg et al. (2023)* compared with that of *Bourdon et al. (2024)*.

As adenomyosis and endometriosis have been suggested to share the same pathophysiology — progesterone resistance induced by high local intra-endometrial oestradiol concentration (*Bulun et al., 2023b*; *Cozzolino et al., 2024a*) — one way of improving ART outcomes for patients with adenomyosis may be to reduce the intra-endometrial oestradiol concentration using a GnRH agonist or aromatase inhibitor, or both, to increase exogenous progesterone support. Importantly, adenomyotic tissue contains aromatase which is capable of converting adrenal androgens into oestrogen, even in the setting of ovarian quiescence induced by GnRH agonist therapy (*Urabe et al., 1989*). In this context, the addition of an aromatase inhibitor may prevent local production of oestrogens. The combination of a GnRH agonist and an aromatase inhibitor through different action mechanisms offers a novel method of reducing local oestrogen production. Importantly, local oestrogen production is crucial for the maintenance of endometrial 'inflammation' which may alter the mechanisms of implantation.

From a mechanistic point of view, a recent retrospective study compared uterine contractions in patients with adenomyosis with those of healthy women in different phases of the menstrual cycle. This demonstrated that women with adenomyosis had a different uterine contraction pattern during the menstrual cycle compared with women without adenomyosis, proposing an aetiologic mechanism for infertility and dysmenorrhoea in patients with adenomyosis (*Rees et al., 2024*). Thus, uterine contraction coordination could provide a possible new avenue to improve fertility in patients with adenomyosis.

FUTURE RESEARCH

Interest and research in adenomyosis have grown remarkably in recent years (*Bulun et al., 2021*; *Chapron et al., 2020a*), and the MUSA criteria and their diffusion represent a major achievement (*Harmsen et al., 2022*; *Van den Bosch et al., 2015*). A common language is now available, and, on this basis, research is expected to provide more uniform evidence, making it possible to have comparable findings and draw more robust conclusions. Undoubtedly, more global quality data are needed to optimize knowledge about the pathogenesis of adenomyosis and its relationship to other pathologies. It is suggested that three main goals should be pursued over the next decade.

First, the type of adenomyosis which interferes with embryo implantation or other reproductive outcomes must be clarified. Studies should not focus exclusively on implantation, but also on other reproductive outcomes, including miscarriage and obstetric complications. Term pregnancy should be considered the most meaningful outcome, as in any other high-quality reproductive study. The methodologies used in the studies by *Neal et al. (2020)* and *Cozzolino et al. (2024b)* to address the impact of adenomyosis on fertility are enlightening, but must be repeated using larger sample sizes (*Cozzolino et al., 2024b*; *Neal et al., 2020*).

Second, the most suitable therapeutic approach to be used in ART for adenomyosis needs to be explored. Although evidence is emerging on the efficacy of using freeze-all strategies, protracted hormonal suppressive treatments, and tailored and high-dose progesterone in adenomyosis, the quality of the evidence is still weak (*Pirtea et al., 2023*), and RCT are warranted. Of utmost relevance, given the uncertainty on the impact of adenomyosis, the results of these studies must present secondary analyses according to the form of the disease and the presence of symptoms (pain or bleeding). Again, studies should not focus exclusively on implantation, but also on other reproductive outcomes, including miscarriage and obstetric complications.

Third, and most ambitiously, the pathogenesis of adenomyosis should be further clarified. This could open the way for treatment options which could prevent the occurrence or spread of the disease. Continuous treatment regimens with progestin or COC initiated in adolescence could be a preventive approach; however high-quality studies are required to validate this (*Vercellini et al., 2024a*,b).

DATA AVAILABILITY

No data was used for the research described in the article.

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AUTHOR CONTRIBUTIONS

The manuscript was written, revised and approved by all co-authors.

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