The association between adenomyosis and infertility

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ABSTRACT

A causal relation between adenomyosis and life-long primary infertility has been documented. This review will address this issue and focus on treatment options.

The advances in radiologic imaging during the last two decades has facilitated the research on the effect of adenomyosis on reproductive outcome. Adenomyosis presents with a set of features on ultrasonography (US) and Magnetic Resonance Imaging (MRI). The severity of adenomyosis, expressed as a score to represent accumulation of ultrasonographic features, is associated with a higher chance of failed IVF–ET, independent of age and ovarian reserve.

However, the evidence showing reduced fertility outcomes related to the presence and the extent of adenomyosis is of low quality.

Furthermore, the lack of standardization for defining adenomyosis and classifying the extent of the disease makes the available findings non-reproducible. The incidence of adenomyosis in the infertile women entering an IVF/ICSI program have been reported between 6.9% to 34.3%. The clinical pregnancy rates, the implantation rates and live birth rates have been reported lower among women with adenomyosis group when compared to controls.

Pretreatment with GnRH agonists before natural conception or embryo transfer after IVF/ICSI cycle should be the management of choice for women with adenomyosis.

Another treatment option could be oocyte / embryo accumulation with consecutive IVF/ICSI cycles and future frozen-thawed embryo transfer after 3-6 months of GnRH-analog treatment.

KEYWORDS

Fertility, adenomyosis, ultrasound diagnosis, IVF, egg harvesting, MRI

Introduction

Myomas, endometriosis, adenomyosis are gynecological disorders that may cause decreased fertility, either individually or as a group. Namely the prevalence of adenomyosis may reach 90% in the subset of women with endometriosis younger than 36 [1-4]. A causal relation between adenomyosis and life-long primary infertility has been documented, even when cases of coexisting endometriosis were excluded [5]. Although most of the reports documented in humans have suggested such a relation they were mostly case series with low level of evidence [6,7]. Moreover, methodology used for the diagnosis is not standardized, ideal clinical trial design is lacking, confounding factors are not adjusted between the treated and non-treated groups, which may have unfortunately compromised the evidence derived from these studies. Besides, in clinical trials researchers have looked at surgical interventions on adenomyosis and fertility outcomes, no sham surgery has been reported that would neutralize biases such as the placebo effect. Nevertheless, the advances in radiologic imaging during the last two decades has facilitated research on the effect of adenomyosis on reproductive outcome. In fact, in order to evaluate the type and extension of adenomyosis, two-dimensional (2D), three-dimensional (3D), and color or power Doppler ultrasound (US) have aided at improving the early and detailed diagnosis of adenomyosis, by clearly delineating the endo-myometrial junction. Despite this, there is no standard for the staging of the disease, and no objective treatment algorithm has been proposed in clinical practice.

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Diagnosis

Different classifications have been published in the literature. One proposed classification divides adenomyosis into diffuse adenomyosis, focal adenomyosis, polypoid adenomyoma and other forms [8]. Focal adenomyosis is subdivided into adenomyoma which is defined by infiltration of myometrium with less clear borders and with mainly solid characteristics, and cystic adenomyosis [8]. The term juvenile cystic adenomyosis (JCA) is reserved for the variant of focal cystic adenomyosis, which is present in women younger than 30 [9]. Polypoid adenomyoma is divided into typical and atypical polypoid adenomyomas [10,11]. The other forms are adenomyomas of the endocervical type and retroperitoneal adenomyomas [12].

Improvements in the components of image processing systems (image sensors, image processing hardware, image processing

software, image display) have made the non-invasive diagnosis of adenomyosis possible and more accurate than ever before. The 2D grayscale US features suggestive of adenomyosis can be summarized as (1) bulky uterus (volume ≥ 100 cc); (2) heterogeneous myometrium; (3) streaky myometrium; (4) myometrial cyst(s); (5) ill-definition of the endometrial-myometrial interface (EMI); and (6) subendometrial echogenic striations (SES), representing echogenic striations extending perpendicular from the endometrium into the inner myometrium [13-15]. All possible dual (15 possible permutations) and triple (20 possible permutations) combinations of these may result in improved diagnosis [16]. Other features reported by 2D-transvaginal US (2D-TVUS) include: hyperechoic or hypoechoic linear striation in the myometrium, sub-endometrial microcysts, asymmetrical myometrial thickening of the uterine wall, thickening of the junctional zone (JZ), and hyperechoic myometrial areas [17-19].

The reproducibility of evaluating the type and extension of adenomyosis using 2D, 3D, and color or power Doppler sonographic features has not been tested. Hence, none of the classifications and schemas have been standardized for clinical practice. Four graded scoring system for mapping the severity of adenomyosis has been proposed. Schematic mapping system defined five types of adenomyosis: 1. diffuse adenomyosis (diffuse inside the myometrium and thickening of the uterine walls); 2. diffuse adenomyosis of the JZ (diffuse inside the JZ and thickening of the JZ); 3. focal adenomyosis (Focal lesions within the outer myometrium); 4. focal adenomyosis of the JZ (focal lesion in the JZ); and 5. adenomyoma [20].

Power Doppler US imaging may be used to differentiate between focal adenomyosis and leiomyomas and between any myometrial cysts or lacunae and vascular components. Translesional vascularity is interpreted as being related with adenomyosis, whereas circumferential vascularity with leiomyomas [21].

Four features of 3D US are used to evaluate the JZ in all uterine walls: 1) maximum JZ; 2) JZ difference; JZ interruption; and sub-endometrial lines and buds. The JZ is thickened if the maximum JZ measures more than 10.5 mm in any of the uterine walls. If the JZ difference (maximum – minimum JZ) measures 5 mm or greater in any wall, the JZ zone is irregular [22]. Tissue strain and stiffness measured by sonoelastography could be used to discriminate myometrium, myomas, and adenomyosis [23]. There was no statistically significant difference found between the different TVUS modalities [24].

Typical magnetic resonance imaging (MRI) parameters in uteri with adenomyosis are the focal or diffuse thickening of the JZ, an area of low-signal-intensity in the myometrium, and high-signal-intensity spots in the T2-weighted resonance [25-27]. Furthermore, the aggregated sensitivity for MRI was reported as 78% (95% CI 70-84), specificity 88% (95% CI 88-92), positive likelihood ratio 6.8 (95% CI 4.54-10), negative likelihood ratio 0.25 (95% CI 0.18-0.35), indicating an overall good test quality for MRI. The overall diagnostic performance of US for detecting adenomyosis compared to MRI has a sensitivity of 36.8% (95% CI 31.5-42.4%), and a specificity of 91.8% (95% CI 88.4-94.6%) [16]. The diagnostic performance of MRI, 2D-TVUS, 3D-TVUS, and TVUS-all showed no statistically significant difference between the various modalities [24].

Association between infertility and adenomyosis

In the majority of cases adenomyosis does not show sharp demarcation with the healthy myometrium. Hence, calculating the affected part of the uterus would become useless and difficult to predict. It has been shown that if the uterus contains four or more ultrasonographic features of adenomyosis, the impact on the chance of clinical pregnancy is significant [28]. In addition, adenomyosis seems to be correlated with endometriosis where it might be present in one-third of women with surgically treated endometriosis [29]. Thus, women with endometriosis should always be carefully examined for imaging methods for the signs of adenomyosis.

The evidence showing reduced fertility outcomes related to the presence and the extent of adenomyosis is based on cohort and case-control studies that are mostly of low quality. Moreover, a lack of standardization for defining adenomyosis and classifying the extent of the disease makes the available findings non-reproducible [30]. Some studies have reported no measurable impact [31,32], while others have found a significant negative effect of adenomyosis on the chance of conception and live birth [33,34]. On the other hand, the prevalence of adenomyosis in a population of infertile women may vary ranging between 7% and 27%.

Adenomyosis was associated with overall reduced pregnancy and birth rates in women who underwent IVF or ICSI [35]. Similarly, in women who underwent surgery for rectovaginal and colorectal endometriosis, the effect of concomitant adenomyosis was a reduction of pregnancy rates, in both spontaneous and assisted reproductive technological pregnancies [35]. Likewise, the risk of miscarriage and preterm delivery in women with adenomyosis has been reported to be higher than in women without the condition [35]. However, it is important to note that one study [36] revealed that discrete sonographic changes, defined by only one image criterion for the diagnosis of adenomyosis in asymptomatic women, may not affect fertility [36].

Factors affecting fertility in cases of adenomyosis can be summarized under 6 headlines. Firstly, aberrant uterine contractility impairing rapid and sustained directed sperm transport could be responsible for infertility linked to adenomyosis. Myometrial contraction patterns during embryo transfer have resulted in lower implantation and pregnancy rates in higher frequency JZ uterine activity and vice versa [37-39]. Yet, evidence is inadequate to definitely consider abnormal myometrial activity during the peri-implantation period as an additional mechanism for reproductive failure in women with adenomyosis.

Secondly, myometrial activity originating from the JZ in the nonpregnant uterus of women with adenomyosis has shown to be altered. In this manner, aberrant uterine contractility impairing rapid and sustained directed sperm transport may be another cause of infertility attributed to adenomyosis [40]. Third, endometrial stroma vascularization has been found to be increased in the secretory phase, while negatively affecting endometrial receptivity and implantation [41]. Fourth, local conversion of androgens to estrogens results in a hyperestrogenic endometrial environment, which sustains the increased expression of estrogen receptors α during the secretory phase, which should have normally declined

under the effect of progesterone. The hyperestrogenic endometrial milieu along with the overexpression of estrogen receptors adversely affect key elements for the development of a receptive endometrium [42].

Fifth, some of the cytokines and growth factors in the endometrium could have altered expressions leading to adenomyosis-associated infertility. While hypoxia-inducible factor 1α (HIF-1α) and interleukins (IL-6, IL-8, IL-10) as well as IL-8 receptors CXCR1 and CXCR2, matrix metalloproteinases (MMP2 and MMP9), and vascular endothelial growth factor (VEGF) seem to be increased, leukemia inhibiting factor (LIF), LIF receptor α, and IL-11 tend to decrease [42]. Lastly, a significant decrease in the expression of HOXA-10 gene during the midluteal phase has been documented in women with adenomyosis [43]. HOXA-10 gene expression peaks during the implantation window and, hence it is considered a necessary component of endometrial receptivity [42,44].

Adenomyosis presents with a set of ultrasonographic features. The severity of adenomyosis, expressed as a score to represent accumulation of ultrasonic features, is associated with increased chance of IVF failure, independent of age and ovarian reserve. Namely, women having four or more features of adenomyosis on US might have lowered chance of pregnancy. Mild forms of adenomyosis have limited impact while more severely affected women have poorer outcomes [28]. The higher the number of visible adenomyosis features on US, the worse the clinical impact on reproductive performance [28]. An endometrial-myometrial junction that is visibly disrupted on US may be a manifestation of a deeper invasion and may impede implantation [42,45]. As the endometrial invasion becomes extensive, clinical pregnancy rate in women with several US features of adenomyosis seems to decrease [28].

Medical therapies

The age of the patient, desire for a future pregnancy, symptoms, and coexisting pelvic diseases should be taken into consideration in order to choose the correct therapeutic strategy for women with adenomyosis [46]. Medical approach to adenomyosis disease is based on its hormone dependent nature and on its similarities to endometriosis. Most frequently used medical treatments for adenomyosis include oral contraceptive combined pill, progestogens, gonadotropin-releasing hormone agonists (GnRH-analogs), levonorgestrel-releasing intrauterine device (LNG-IUD) [47-49]. Medical treatment only induces disease regression but not eradication of the pathology, in a similar fashion as treatments for endometriosis.

The incidence of adenomyosis in the infertile women entering an IVF/ICSI program were reported between 6.9% to 34.3%. Clinical pregnancy rates in women with adenomyosis were found to be lower when compared to controls. Similarly, implantation rates and live birth rates were reported lower in the adenomyosis group than those of controls [50]. Miscarriage rate per clinical pregnancy was also significantly increased in women with adenomyosis. However, no significant difference was documented when analysis was restricted to women undergoing a single IVF/ICSI cycle. Interestingly, coexistence of endometriosis did not alter these results [50].

Published risk ratios for successful IVF–ET treatment in women with adenomyosis have ranged between 0.37 and 1.20 [51,52]. The unstandardized criteria used for the diagnosis of adenomyosis by different authors is most likely the cause of this wide variation of fertility success. In order to examine the impact of each ultrasonographic feature of adenomyosis on clinical pregnancy, a dummy variable for each level (score 0–7) was created and the equal weight of each feature was later tested to support this assumption [28].

Women diagnosed with adenomyosis on US scan were compared with those with normal uteri. Even though women with adenomyosis were older and had lower anti-Mullerian hormone (AMH) levels compared to those with normal uteri, there were no differences in body mass index, antral follicle count (AFC), baseline FSH level and total dose gonadotrophin used when comparing women with and without adenomyosis [28]. Women with any feature of adenomyosis were significantly less likely to have a clinical pregnancy following ET. Logistic regression determined AFC (1.07, 95% CI 1.03–1.10) and accumulation of four or more US features (OR 0.35, 95% CI 0.15–0.82) as significant predictors of clinical pregnancy. Even calculated probability of clinical pregnancy for each level of adenomyosis score were determined [28]. However, it is not clear yet whether some US features of adenomyosis were more deleterious than others.

Fertility outcomes in adenomyosis patients undergoing frozen ET after long-term preparation of the endometrium with GnRH-analog therapy have been compared to women not pretreated with GnRH-analog. Clinical pregnancy, implantation, and ongoing pregnancy rates were significantly higher in women pretreated with GnRH-analog [53]. Nevertheless, in another study GnRH-analog pretreatment resulted in higher but non-significant improved pregnancy rates [54]. The beneficial effect of GnRH-analog therapy would be to produce a window of time with improved implantation. Therefore, GnRH-analog pretreatment before natural conception or embryo transfer after IVF/ICSI cycle should be suggested in women with adenomyosis [30].

One set back would be for women with adenomyosis who are in their later reproductive years, and with reduced ovarian reserves. This group of women should not delay their fertility treatments, and should undergo immediate IVF or ICSI with oocyte retrieval in repetitive cycles in order to harvest enough oocytes for freezing. After a couple of oocyte retrievals, women are given 3-6 months of GnRH-analog treatment before a frozen-thawed embryo transfer (FET) is performed [54]. Women with normal ovarian reserves and adenomyosis may also benefit from the egg harvesting. However, women with discrete adenomyosis and a normal ovarian reserve are likely to have marginal decreased fertility. They may attempt a fresh ET with or without 3 months of GnRH-analog pretreatment [30].

Surgical therapies

Considering the relevant technical progress seen in recent years and the increasing rate of preoperative diagnosis of adenomyosis, it is currently possible to perform a "tailored" treatment for any patient, based on the several available medical and surgical options [46].

In cases where the surgical approach is chosen, it is necessary to accurately define the characteristics of the adenomyosis in order to perform a "tailored" treatment. The concept of conservative "uterine-sparing" surgery (either performed by laparoscopy/laparotomy or hysteroscopy) for adenomyosis is increasing as fertility preservation and quality-of-life improvement can be achieved in this group of patients [55,56].

The surgical technique for the excision of focal adenomyosis is similar to myomectomy in many technical aspects, whether by laparotomy or laparoscopy. However, it can be challenging since adenomyosis generally lacks a cleavage plane. When the adenomyotic lesion can be clearly defined preoperatively, laparoscopy is a feasible technique [57].

Diffuse adenomyosis characterized by lesions with unclear borders, may not allow complete excision of adenomyotic tissue, and even worse, it might cause the loss of healthy myometrium. In these cases, the laparotomic approach should be chosen. By digital palpation of the uterus, the involved areas are better delineated, and the excision of healthy myometrium is prevented. Preservation of at least 1–1.5 cm of myometrial thickness is needed for uterine reconstruction. Nevertheless, this might not be probable after an extensive excision. Multiple layers of interrupted sutures should be applied for good recovery and uneventful obstetrical outcome [58].

In cases of superficial adenomyotic nodules > 1.5 cm in size and for diffuse superficial adenomyosis, hysteroscopic resectoscopy is the choice of treatment [46]. On the contrary, hysteroscopic approach should not be chosen for managing deep adenomyosis (endometrial penetration of >2.5 mm) [59]. Using resectoscopic treatment for focal adenomyosis, the technique of adenomyomectomy merits several steps. Tissue protruding into the uterine cavity is incised, evacuated, and resected (by slicing) using a resectoscope with a cutting loop. In cases of deeply implanted lesions, the nodule may first be mobilized and then pulled into the uterine cavity. These techniques are similar to those used for the treatment of a submucosal myoma with an intramural component. Coagulating the implantation base of the lesion concludes the surgical procedure [46].

The goal of surgery is to remove all adenomyotic tissue without harming the surrounding healthy myometrium. However, the surgical procedure might be quite challenging due to the lack of a distinct cleavage plane next to the normal myometrial tissue [60,61]. The level of intramural extension of the pathology is correlated with the technical difficulty and risks of the procedure. With the assistance of US during the procedure, extreme care must be taken regarding the thickness of the myometrium between the outer margin of adenomyosis and the uterine serosa. It is worth noting that endomyometrectomy may give rise to dissemination and proliferation of ectopic endometrial cells, promoting progression of the pathology and "de novo" adenomyosis [46].

For patients with focal disease and for selected cases of more diffuse adenomyosis, excision of the adenomyoma or cystectomy for cystic focal adenomyosis can be proposed [8]. Besides partial removal of the abnormal tissue, cytoreductive surgery is reserved for cases of diffuse adenomyosis with special attention at preserving a functional uterus [8].

Surgery should only be considered for symptomatic women with repeated IVF/ICSI failure after the transfer of high-quality embryos [30]. A pregnancy rate of 47%, delivery rate of 37%, and miscarriage rate of 10% have been reported after surgery for adenomyosis in 338 women with adenomyosis who tried to conceive [35]. The delivery rate was even higher (50%) for cases in which complete excision of localized adenomyosis was performed in younger women. Still, surgery would not be appropriate for women > 40 because they would have a very low pregnancy rate [62] even after cytoreductive surgery.

Conclusion

The evidence regarding the degree of endomyometrial involvement related with fertility is poor. The type and extent of adenomyosis that may reduce implantation has not yet been fully defined. Mathematical programming models using US parameters should be constructed for the prediction of fertility probabilities for different types of adenomyosis [24].

It is evident that more studies are needed to gather good evidence before tailored treatment for individual women be recommended, based on the extent of their disease. For this reason, the treatment effect (adenomyosis versus no adenomyosis) has to be determined firstly. Secondly, the prevalence of adenomyosis in a given population needs to be known. Thirdly, a drop-out and loss to follow-up of at least 15% patients should be taken into consideration [28].

The limited evidence on improved fertility outcome with currently available treatment options suggests GnRH-analog pretreatment before natural conception or embryo transfer after IVF/ICSI cycle. Women with adenomyosis who have poor ovarian reserves, or have bilateral endometriomas [63], should attempt immediate oocyte retrieval in consecutive IVF/ICSI cycles and freeze their eggs/embryos for future frozen-thawed embryo transfers. Symptomatic women with repeated IVF/ICSI failure after high-quality embryo transfers could be offered surgery.

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Conflicts of interest

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