RMMG
Revista Médica de Minas Gerais

REVIEW ARTICLE

Adenomyosis and your implications on fertility and on the results of assisted reproduction techniques (ART)

Adenomiose e suas implicações sobre a fertilidade e sobre os resultados das técnicas de reprodução assistida (TRA)

Laura Bonfim Viana[1], Lucas Barbosa de Lima[1], Laura Magalhães dos Santos Amaral[1], Samira Olivé Domingos[1], Maria Clara Magalhães dos Santos Amaral[2], Ana Márcia de Miranda Cota[2]

ABSTRACT

Introduction: Adenomyosis is a benign invasion of the endometrium into the myometrium, which produces an enlarged uterus with ectopic endometrial glands and stroma surrounded by the myometrium, with hyperplastic and hypertrophic changes. This condition has characteristic symptoms such as abnormal uterine bleeding, dysmenorrhea, chronic pelvic pain, miscarriage, and infertility. **Objective:** To assess the relationship between adenomyosis and infertility, as well as its possible impact on the outcomes of assisted reproductive technology. **Methods:** It is a review, with articles searched in the PubMed, UpToDate and SciELO databases, in Portuguese and English, published from 1989 to 2021. **Results:** Currently, the diagnosis of adenomyosis is made by imaging tests, which allow the early diagnosis in young women and makes it possible to investigate the relationship between adenomyosis and infertility. This relationship has not yet been established, but several theories have been proposed, such as impaired tubal transport, decreased sperm function related to nitric oxide levels in the uterine cavity, impaired embryo implantation, and altered uterine contractility. Furthermore, outcomes of assisted reproduction techniques and pregnancy outcomes appear to be affected, with studies showing lower rates of implantation and pregnancy, as well as higher rates of miscarriage and preterm birth. **Conclusion:** Although adenomyosis has negative impacts on women's fertility and on the abortion rate, more studies and research are needed to, for example, define diagnostic criteria and create protocols for approaching adenomyosis.

Keywords: Adenomyosis; Infertility; Reproduction.

[1] Faculdade Ciências Médicas de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil.

[2] Centro de Reprodução Humana da Rede Mater Dei de Saúde, Belo Horizonte, Minas Gerais, Brazil.

Responsible Editor:
Dr. Frederico Duarte Garcia
Faculdade de Medicina da Universidade Federal de Minas Gerais.
Belo Horizonte/MG, Brazil.

Corresponding Author:
Ana Márcia de Miranda Cota
E-mail: anamarcia.cota@gmail.com

Conflict of Interest:
None.

Received on: May 15, 2023.
Accepted on: November 08, 2023.
Publication Date: March 07, 2024.

DOI: 10.5935/2238-3182.2022e33212-en

RESUMO

Introdução: A adenomiose é uma invasão benigna do endométrio no miométrio, que produz um útero aumentado com glândulas endometriais ectópicas e estroma circundado pelo miométrio, com alterações hiperplásicas e hipertróficas. Essa condição tem sintomas característicos como sangramento uterino anormal, dismenorreia, dor pélvica crônica, aborto espontâneo e infertilidade. **Objetivo:** Avaliar a relação entre a adenomiose e a infertilidade, além do seu possível impacto nos resultados da tecnologia de reprodução assistida. **Métodos:** É uma revisão, com artigos pesquisados na base de dados PubMed, UpToDate e SciELO, em português e inglês, publicados no período de 1989 a 2021. **Resultados:** Atualmente, o diagnóstico da adenomiose é feito por exames de imagem, que permitem o diagnóstico precoce em mulheres jovens e possibilita a investigação da relação entre adenomiose e infertilidade. Essa relação ainda não foi estabelecida, porém diversas teorias têm sido propostas, como o prejuízo no transporte tubário, a diminuição da função espermática relacionada aos níveis de óxido nítrico na cavidade uterina, a implantação prejudicada do embrião e a alteração da contratilidade uterina. Ademais, os resultados das técnicas de reprodução assistida e os resultados da gravidez parecem ser afetados, com estudos apresentando taxas mais baixas de implantação e de gravidez, além de taxas mais altas de aborto espontâneo e parto prematuro. **Conclusão:** Ainda que a adenomiose proporcione impactos negativos na fertilidade das mulheres e na taxa de abortamento, é preciso mais estudos e pesquisas para, por exemplo, definir critérios de diagnóstico e criar protocolos de abordagem à adenomiose.

Palavras-chave: Adenomiose; Infertilidade; Reprodução.

Introduction

Adenomyosis was defined in 1972 as a benign invasion of the endometrium into the myometrium, producing a diffusely enlarged uterus with ectopic endometrial glands and stroma surrounded by myometrium, with hyperplastic and hypertrophic alterations. It generally affects women aged 40 to 50 years, but can be found incidentally in younger women, and it may coexist with other gynecological conditions, such as endometriosis and uterine fibroids[1].

Although 35% of affected women are asymptomatic at the time of diagnosis, the rest may experience some symptoms such as abnormal uterine bleeding, dysmenorrhea, dyspareunia, chronic pelvic pain, miscarriages, and infertility[1]. For many years, the diagnosis of adenomyosis was made by histopathological examination of hysterectomy. Today, with the improved resolution of transvaginal ultrasonography (TVUS) and/or magnetic resonance imaging (MRI), earlier and non-invasive diagnosis is possible with accuracy of 80% to 90%[2].

Diagnostic imaging has improved the understanding of adenomyosis and allowed for earlier diagnosis in younger women, making it possible to investigate the relationship between adenomyosis and infertility[3]. This relationship, however, is not yet fully established. Several theories have been proposed, including impaired utero-tubal transport, reduced sperm function due to high levels of nitric oxide in the uterine cavity, impaired embryo implantation, altered uterine contractility, and many others. Furthermore, the outcomes of assisted reproductive techniques seem to be impaired, as well as pregnancy prognosis, with some studies demonstrating lower rates of implantation and pregnancy, and higher rates of miscarriage and preterm birth[4,5].

The purpose of this review is to evaluate the relationship between adenomyosis and infertility, and its possible

implications on the results of assisted reproductive techniques (ART).

Methods

This is a literature review based on articles found in the PubMed, UpToDate and SciELO databases. The descriptors used in English and Portuguese were: "adenomyosis" and "infertility". The inclusion criteria used were set to choose papers in Portuguese and English, published from 1989 to 2021, including literature reviews, clinical protocols, books and original articles, full text available. Duplicate studies, abstracts, and those in the approval process were excluded. The results were presented descriptively (Table 1), divided into categories that included: introduction, correlation between adenomyosis and infertility, impact of adenomyosis over reproductive outcomes, and adenomyosis treatments.

Results

Correlation between adenomyosis and infertility

Until recently, the diagnosis of adenomyosis was most often made by an anatomical and pathological study based on hysterectomies. The pathology was then related to multiparous women, and not to infertility. With recent advances in imaging techniques, the diagnosis has now been made by transvaginal ultrasound and MRI, which has made it possible to see the women conditions other than just multiparous women, including nulliparous and infertile women, allowing the relationship between adenomyosis and infertility to be observed and studied[6].

One third of women with adenomyosis are infertile (Bourdon et al., 2020). A systematic review showed a 28% decline in pregnancy rate in patients with adenomyosis submitted to IVF, and an increase in miscarriage rate[1].

There are several mechanisms proposed to link adenomyosis and infertility. Among them are the anatomical distortions caused themselves by the disease, such as the overall increase in uterine volume, the presence of intramural adenomyomas that distort the endometrial cavity; abnormal uterine contractility; changes in endometrial vascularization and histology; inflammatory, molecular, and hormonal endometrial alterations[7].

The presence of myometrial contraction waves is physiological and visible on the ultrasound. This peristaltic activity is what helps out with the transport of sperm towards the fallopian tubes, which is fundamental in the initial reproductive process, and it depends on the architecture of the myometrial wall and its circular muscle fibers[8]. In adenomyosis patients, the invagination of endometrial glands and stroma in the myometrium leads to hyperplasia of the muscle tissue culminating in peristaltic dysfunction and increased intrauterine pressure. Also, the junctional zone (JZ) - a layer of myometrium that is adjacent to the endometrium - in women with adenomyosis shows nuclear and cellular hypertrophy, mitochondrial changes and other ultrastructural alterations that may lead to calcium channel dysfunction with subsequent loss of rhythmic contraction and that may alter uterine-tubal transport[8].

During the peri-implantation period, the myometrial activity must be kept at a minimum level to facilitate the apposition, adhesion, and penetration of the embryonic pole of blastocyst into the decidualized endometrium[7]. Research focusing on myometrial contraction patterns during the embryo transfer has demonstrated lower pregnancy and implantation rates in patients who show a higher frequency of uterine junctional zone activity[9].

The currently most accepted theory to explain the histological phenomena is that basal endometrial glands invade the underlying myometrium, causing intrinsic adenomyosis, affecting the JZ as well as the myometrium[1] Piver proposed that MRI evaluation of JZ thickness is the best predictive negative factor of implantation failure, and an increase in its diameter is inversely related to the implantation rate. It was seen that implantation failure was elevated when the JZ average was higher than 7 mm. Also, the endometrial receptivity seems to be compromised due to the extremely increased vascularity in the secretory phase, which may negatively affect the implantation rates[11].

Some ultrasonographic criteria regarding patients with adenomyosis showed a negative correlation between results of assisted reproduction treatments[12]. It was attributed a lower success rate after the IVF, the higher the number of criteria identified in the patient. The criteria described were: asymmetry of myometrial wall thickness (A), parallel shadows (B), linear striations (C), myometrial cysts (D), hyperechogenic islands (E), adenomyomas (F), and irregular myometrial endometrial junction (G) (Figure I).

A study on the molecular phenomena demonstrated a decreased endometrial receptivity and an impaired decidualization in adenomyosis associated with alterations in gene expression of HOXA10 (a necessary component of endometrial receptivity with a spike in the implantation window), in LIF (leukemia inhibitory factor), MMP (metalloproteinases), interleukins (IL-6, IL-8 and IL-10), among others[13]. Meanwhile found a correlation between down regulation of FOXO1A in adenomyotic tissue and inadequate decidualization, which could compromise the embryo implantation in patients with adenomyosis[14]. However, there is still not enough research to prove whether these changes can be restored with the use of progesterone during the implantation window[15].

The abnormal inflammatory response has been much studied. Macrophages can produce not only pro-inflammatory cytokines such as TNF-α (tumor necrosis factor alpha) and IL-1, but also free radicals that can be toxic to embryos[16]. Noticed that women with severe adenomyosis, who had embryo implantation failure, showed an increase in macrophage density compared to control patients. In the case of adenomyosis, there is also an increased expression of IL-1b and CRH (corticotropin-releasing hormone) in the ectopic endometrial tissue[17]. Reported an increased in inflammatory response in the

Table 1. Results of the main studies included in this review.

Author	Year	Kind of research	Results
Younes and Tulandi[2]	2017	Meta analysis	Implantation rates, clinical pregnancy per cycle, clinical pregnancy per embryo transfer, ongoing pregnancy and live births among women with adenomyosis were significantly lower than those without adenomyosis. The spontaneous abortion rate in women with adenomyosis was higher than in those without adenomyosis. It appears that surgical or GnRHa treatment increases the rate of spontaneous pregnancy in women with adenomyosis.
Huang et al.[28]	2012	Retrospective study	Postoperative follow-up showed that the intensity of dysmenorrhea improved significantly. The improvement scale was positively correlated with a decline in serum CA125 level. A postoperative serum CA125 reduced to less than 10.00 IU/mL correlated with an improved spontaneous pregnancy rate, especially during therapy.
Won et al.[29]	2021	Retrospective study	43 patients who underwent adenomyomectomy and who wished to become pregnant post-operatively were included in the study. The pregnancy success rate was 34.9%.
Niu et al.[30]	2013	Retrospective study	339 patients with adenomyosis were included in the study. Of these, 194 received GnRH agonist plus HRT (hormone replacement therapy) and 145 received HRT alone. There were no differences between groups in characteristics such as age, body mass index, duration or cause of infertility, serum CA-125 level and baseline hormone levels. On the day of progesterone administration, mean endometrial thickness and serum progesterone level were significantly higher in HRT patients. In the aGnRH + HRT group, the rates of clinical pregnancy, implantation, and ongoing pregnancy were 51.35%, 32.56%, and 48.91%, respectively, significantly higher than those in the HRT group (24.83%, 16.07% and 21.38%, respectively). Thus, it was concluded that GnRH agonist pretreatment significantly improved pregnancy outcomes in patients with adenomyosis.
Park et al.[31]	2016	Retrospective study	Pretreatment with GnRH agonist increased the duration of stimulation (11.5±2.1 days vs. 9.9±2.0 days) and the total gonadotropin dose (3,421±1,141 IU vs. 2,588±1,192 IU), which resulted in a significantly greater number of oocytes recovered (10.0±1,192 IU). 8.2 vs. 7.9±6.8, p=0.013) in group B (fresh embryo transfer with GnRH-a pretreatment) than in group A (fresh embryo transfer without GnRH-a pretreatment). Controlled ovarian stimulation for freezing resulted in a significantly greater number of oocytes retrieved (14.3±9.2 vs. 10.0±8.2, p=0.022) with a lower dose of gonadotropin (2,974±1,112 IU vs. 3,421 ±1,141 IU, p=0.037) in group C than in group B. The clinical pregnancy rate in group C (39.5%) tended to be higher than in groups B (30.5%) and A (25.2%), but without significant difference.
Donadio et al.[32]	2006	Randomized clinical trial	After treatment with the application of a levonorgestrel-releasing intrauterine device, there was a reduction in 77.7% of cases of focal adenomyosis, in addition to a significant reduction in uterine volume and the average thickness of the junctional zone from 128.8 to 93.6 mL and 12.3 to 11.3 mm, respectively. In the IUD group, the pregnancy rate reached 30%, a higher value, although not significantly, than that found in the FIV group, 17.5%.

continued...

...continued Table 1

Table 1. Results of the main studies included in this review.

Author	Year	Kind of research	Results
Osuga et al.[33]	2017	Randomized clinical trial	There was a significant reduction in the pain score and visual analogue scale at the end of treatment in the group that used dienogest (DNG) when compared with the placebo group (P<0.001). During the treatment period, almost all patients treated with DNG experienced irregular uterine bleeding and one patient experienced mild anemia. No serious cases of anemia were observed.
Bourdon et al.[21]	2020	Observational study	A total of 496 women were included in the study population. Three groups were compared: a group without infertility (n = 361), a group with primary infertility (n = 84), and a group with secondary infertility (n = 51). Among them, 248 women did not have adenomyosis lesions and 248 women had a radiological diagnosis of adenomyosis. The presence of FAOM (focal adenomyosis of the external myometrium) was significantly associated with primary infertility. Diffuse adenomyosis has not been associated with infertility. The distribution of endometriosis or leiomyomas was not significantly different between groups. After a multinomial regression model including women's age and associated endometriosis or leiomyoma, the presence of FAOM was identified as an independent associated factor of primary infertility (adjusted odds ratio 1.9; 95% confidence interval 1.1-3 ,3).
Piver[10]	2005	Cohort Study	Women with adenomyosis who became pregnant in IVF cycles had a mean junctional zone (AJZ) value of 5.1mm compared to 6.3mm in non-pregnant women (p < 0.0001). Similarly, pregnant women had a significantly lower maximum junctional zone (MJZ) value than non-pregnant women (6.2 mm versus 9.8 mm, p < 0.0001). For patients with MJZ less than 10 mm, pregnancy rates were 45% per transfer. For those with an MJZ between 10 and 12 mm, the transfer pregnancy rate was 16%. Finally, for women with an MJZ greater than 12 mm, the transfer pregnancy rate was 5%. This influence of junctional zone thickness was independent of age. After logistic regression, it was found that the association of AJZ > 7 mm and MJZ > 10 mm is a risk factor for IVF failure (absence of pregnancy). This relationship is highly significant (p = 0.0007) with an OR of 32 and a confidence interval between 4.2 and 241, meaning that abnormal thickness of the junctional zone is recognized as a cause of pregnancy failure in IVF, and much more than a simple risk factor.
Vercellini et al.[4]	2014	Systematic review and meta-analysis	In the five selected observational studies, in women seeking pregnancy, 11.9% women with concomitant adenomyosis became pregnant, compared with 74/172 (43.0%) in those without adenomyosis. One in 10 women undergoing surgery for rectovaginal and colorectal endometriosis had a serious surgical complication. The RR of clinical pregnancy consistently ranged from 0.23 to 0.46 after surgical resection. Adenomyosis was associated with a 68% reduction in the likelihood of pregnancy in women trying to conceive after surgery for rectovaginal and colorectal endometriosis.

continued...

...continued Table 1

Table 1. Results of the main studies included in this review.

Author	Year	Kind of research	Results
Chiang et al.[24]	1999	Clinical trial	Age, day 3 follicle stimulating hormone, antral follicle count, ovarian response, endometrial thickness, number of oocytes retrieved and fertilized, number of embryos transferred, clinical pregnancy rate, and full birth rate were not were statistically different between the two groups, one with patients with a sonographically, diffusely enlarged uterus without distinct uterine masses and the other with patients with a normal uterus (P < 0.05). Patients with a sonographically diffuse enlarged uterus without distinct uterine masses had a higher miscarriage rate (66.7%) than controls (P < 0.04; odds ratio = 7.5; 95% confidence interval, 1.16-48.56).
Mijatovic et al.[25]	2010	Retrospective cohort study	Study evaluated 74 women who underwent IVF/ICSI. Adenomyosis was demonstrated in 27% of them and was predominantly located on the posterior wall of the uterus. No significant differences were found for any of the IVF/ICSI outcomes (number of embryos, fertilization rate, implantation rate, clinical pregnancy rate, and miscarriage rate) between women with and without adenomyosis.
Thalluri et al.[26]	2012	Retrospective cohort study	The presence of adenomyosis diagnosed by ultrasound was associated with a significant reduction in the successful implantation of good quality embryos in patients undergoing GnRH antagonist stimulation for IVF treatment (clinically viable pregnancy rate 23.6% versus 44. 6%, P = 0.017). However, the median maternal age and duration of infertility of the adenomyosis group were 2 years older and 4 months higher, respectively, than those of the non-adenomyosis group. A logistic regression analysis was performed to explain these differences between the two groups, with the adjusted results still showing a statistically significant decline in the viable pregnancy rate in the adenomyosis group (OR = 0.408, CI = 0.181-0.922, P = 0.031 when adjusted for maternal age; OR = 0.417, CI = 0.175-0.989, P = 0.047 when adjusted for duration of infertility). The results of this study should be representative of the results of any patient undergoing a cycle of GnRH antagonist ovarian stimulation for IVF, as standard IVF treatment protocols were used.
Martínez-Conejero et al.[27]	2011	Retrospective cohort study	Endometrial samples were analyzed using microarrays in women with adenomyosis and healthy controls. The clinical study included three groups: adenomyosis, endometriosis and control. There is a similar endometrial gene expression pattern in both the adenomyosis group and the control group, and non-parametric tests revealed 34 dysregulated genes in adenomyosis patients, but none belonged to the implantation window gene group. Egg donation implantation did not differ between the three groups. However, miscarriage was significantly higher in the adenomyosis group versus the adenomyosis + endometriosis and control groups. The full-term pregnancy rate was also significantly lower in the adenomyosis group compared to others.

endometrium due to the presence of an elevated level of the expression of pro-oxidatives and anti-oxidatives such as Cu, Zn-SOD and Mn-SOD. Other studies confirmed these data by investigating the concentration of nitric oxide in the endometrium, macrophage activity, and IL-6[18]. An increased expression of cytochrome P450 aromatase (P450 aromatase) in the endometrium has also been suggested as a possible mechanism that negatively affects implantation in women with adenomyosis[7]. The aromatase of the P450 chromosome is an enzyme that catalyzes the conversion of androgens to estrogens. The hyperestrogenic microenvironment maintains the expression of the α estrogen receptor increased during the secretory phase that should normally have decreased under the effect of progesterone. Early publications confirmed higher estrogen levels in menstrual blood in adenomyotic women and an increase in aromatase expression of cytochrome P450 in the endometrium, respectively[19,20].

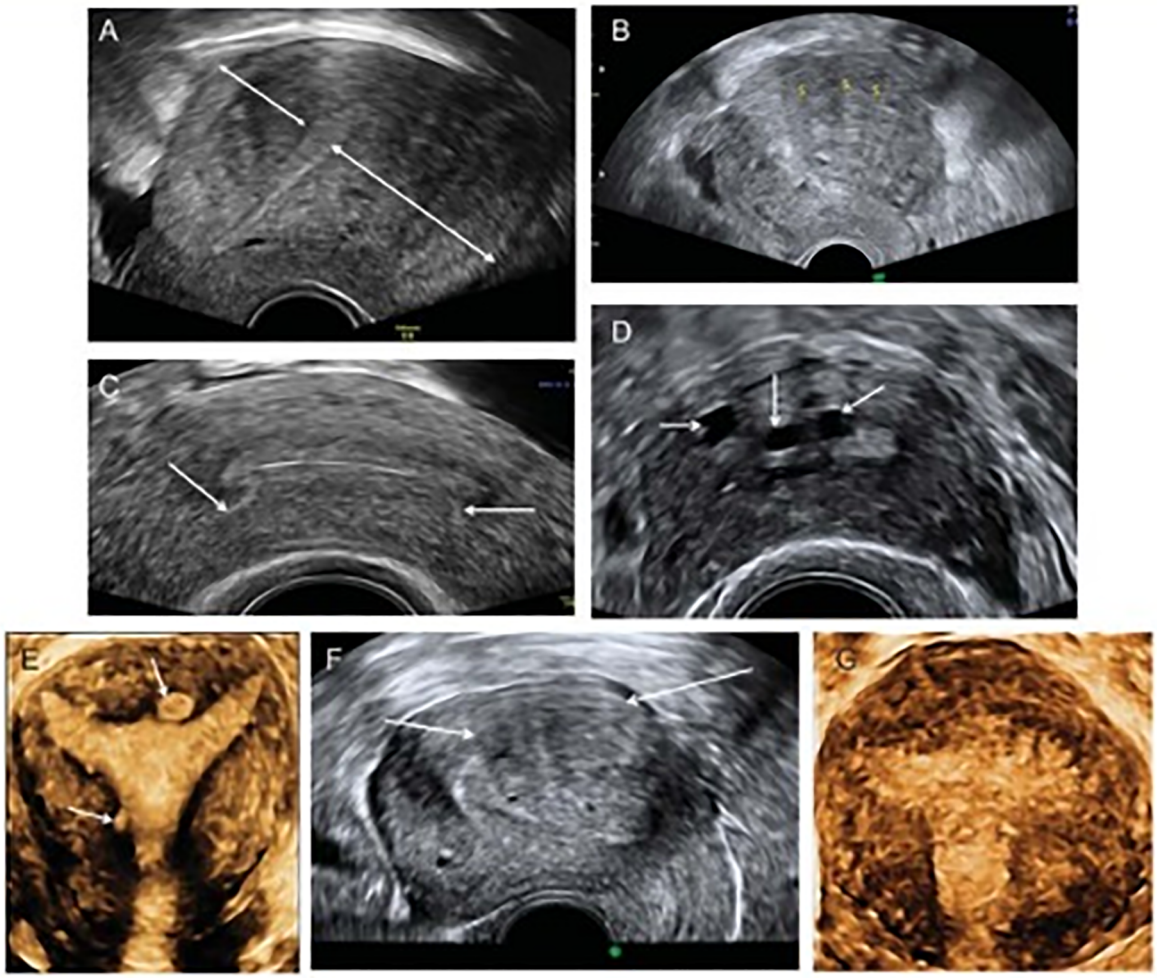


Figure 1. Ultrasound criteria for adenomyosis.

Integrins are the best known and well-studied markers of endometrial receptivity. They are transmembrane receptors that, besides being responsible for endometrial receptivity, activate signaling pathways and mediate cell signaling, such as cell cycle regulation. Abnormal expressions of some integrins, such as β-3 and osteopontin (OPN) were found in patients with adenomyosis, and it was suggested that this expression was responsible for IVF failures, even with good quality embryos. The influence of GnRH analogues on integrin expression and endometrial receptivity have already been described in animals but cannot be conclusive in human pathology[15].

There are still many questions about the relationship of adenomyosis with infertility. This is mainly due to the different classifications of the disease, as well as the mixed profiles of patients (focal and diffuse adenomyosis), which makes more precise conclusions difficult. In all women affected by adenomyosis (focal, diffuse or an association of the two types) the prevalence of infertility is 30.2%, 19.8% being primary infertility and 10.5% secondary[21].

Therefore, from the studies cited above and many others existing in the literature on the subject, it is possible to affirm that there is probably a relationship between adenomyosis and infertility. This relationship is due to molecular and histological phenomena, which are not yet fully understood, being necessary that more studies that are methodologically adequate can be carried out. The elucidation of the relationship between adenomyosis and infertility will provide a better understanding of the lower pregnancy rates in patients of adenomyosis, including those submitted to assisted reproduction treatments, besides the development of possible therapeutic interventions and strategies during the treatments seeking improvement in the results.

Impact of adenomyosis on reproductive outcomes

Recent studies have shown that adenomyosis negatively affects fertility, besides increasing the risk of obstetric complications, such as miscarriage, preterm delivery, and the premature rupture of amniotic membranes[22]. However, there are still few studies evaluating the impact of adenomyosis on reproductive outcomes of assisted reproductive techniques, such as implantation rate, pregnancy rate, and live birth rate[23].

Younes and Tulandi (2017)[2] demonstrated in their meta-analysis, which evaluated 15 studies, that women with adenomyosis had a worse outcome in IVF cycles. Patients with adenomyosis who were submitted to IVF had significantly lower implantation, clinical pregnancy,

evolving pregnancy, and live birth rates when compared to women without adenomyosis. The odds ratio for clinical pregnancy rate when comparing women with adenomyosis and women without adenomyosis submitted to IVF was 0.73, 95%CI=0.60-0.90. Meta-analysis demonstrated that the presence of adenomyosis was associated with a 41% reduction in live birth rate (OR=0.59, 95%CI=0.42=0.82). Further, the group of women with adenomyosis had a significantly higher miscarriage rate (OR=2.2, 95%CI=1.53-3.15). These data are in line with a previous systematic review and meta-analysis[4] that showed a clinical pregnancy rate of 40.5% for women with adenomyosis submitted to IVF compared to 49.8% in women without adenomyosis (RR=0.72, 95%CI=0.55-0.95).

Chiang et al. (1999)[24] studied the relationship of miscarriage rate and JZ dysfunction in infertile patients submitted to IVF and concluded that the rate was higher in women with a diffusely enlarged uterus on ultrasound without distinct uterine masses compared to those with a normal sized uterus. In contrast, Mijatovic et al. (2010)[25] observed no significant differences in pregnancy rates in infertile patients with adenomyosis in association with endometriosis who were pretreated with long-acting GnRH agonist. Furthermore, Thalluri e Tremellen (2012)[26] noticed significantly lower clinical pregnancy rates in patients submitted to IVF with adenomyosis in cycles that used the antagonist protocol of GnRH when compared to patients without adenomyosis (23.6% vs. 44.6%, p=0.017).

In a study evaluating ovoreception cycle, it was observed that women with adenomyosis had double the risk of miscarriage when compared to the group of women without adenomyosis, indicating an impact on pregnancy outcome[27].

Treatments for adenomyosis

The treatment of adenomyosis is still discussed and questioned by several experts, and the clinical treatment and surgical approach are among the methods of choice for possible therapy of this pathology[28]. The decision between clinical or surgical approach will depend on the symptoms presented by the patient and the desire or not for pregnancy.

Drug treatment for adenomyosis can be used for the relief of symptoms such as dysmenorrhea and abnormal uterine bleeding. Among the clinical approach, we have non-steroidal anti-inflammatory drugs (NSAIDs), oral hormonal contraceptives, progestins, progesterone-releasing intrauterine devices, and gonadotropin-releasing hormone agonist. On the other hand, the definitive treatment for adenomyosis is hysterectomy. However, for patients who desire pregnancy, drug treatment or hysterectomy cannot be adopted[29].

Oral hormonal contraceptives are a great option for reducing abnormal uterine bleeding, as well as reducing dysmenorrhea by inducing decidualization, which may result in amenorrhea due to endometrial atrophy. However, there are still few studies evaluating the impact of oral hormonal contraceptive use in patients with adenomyosis and its relationship to the future fertility of these patients[23].

Another drug treatment option used is gonadotropin-releasing hormone agonist (GnRHa)[2]. This drug's main action is to reduce adenomyosis macroscopically and microscopically and decrease clinical effects, such as normal bleeding, pain, and infertility[30]. GnRHa has an antiproliferative effect on endometrial tissue, induces apoptosis, and reduces inflammatory reaction and angiogenesis, helping in the regression of the disease[2]. Importantly, this strategy has resulted in some case reports of successful pregnancy and delivery in women submitted to this treatment[28]. A disadvantage of using this medication is that it has a transient effect, therefore, it is priced to be used as a preoperative adjunctive therapy in surgical treatment[28]. In their meta-analysis, Younes e Tulandi (2017)[2] concludes that the use of GnRHa prior to IVF appears to be beneficial for the pregnancy rate in women with adenomyosis. However, this result was based on only two studies[30,31]. As such, more studies become necessary to confirm this potentially beneficial effect of using GnRHa prior to the IVF cycle.

The levonorgestrel intrauterine device (IUD) has been emerging as a new option for the conservative treatment of adenomyosis[32]. Randomized studies that evaluated the use of the device in women with adenomyosis associated with menorrhagia have demonstrated a significant reduction in both uterine volume and average thickness of the JZ. Its clinical effects show satisfactory results in the control of dysmenorrhea and menorrhagia symptoms, as well as reports of spontaneous pregnancy after its use[23,32].

The dienogest (DNG), which is a 19-norsteroid progestational derivative, is a synthetic oral progestin with highly selective attachment to progesterone receptors, has been pointed out as a new therapeutic alternative for the subgroup of patients with adenomyosis and pelvic pain. This drug has mild anovulatory and hypoestrogenic effects, and antiproliferative activity in human endometrial cells. Based on this hormonal profile, DNG is used as a treatment for pain symptoms in patients with endometriosis. Therefore, some studies have shown an efficacy and good tolerability of DNG in patients with adenomyosis and an algic complaints[33].

Surgical treatment can be divided into a conservative approach reserved for focal adenomyosis or adenomyoma[2] or hysterectomy. However, for obvious reasons hysterectomy is not a therapeutic option for infertile patients or those who wish to preserve their fertility. For this patient profile, conservative surgery may be a therapeutic option. However, the data available in the literature are still controversial and insufficient, mainly because most of the published studies were not designed for this purpose.

Surgical excision (laparoscopic or laparotomy) of adenomyoma or focal adenomyosis aims to preserve the uterus in order to preserve the future fertility of the patient, as well as significant improvement of dysmenorrhea[28].

However there are some drawbacks in the choice of surgery, such as: difficulty in selecting a good candidate to submit to this surgical approach (problem to determine the extent of adenomyosis in a given patient), possible failure to completely eliminate adenomyosis and postoperative sequelae, such as pelvic adhesions, syncytial formation in the endometrial cavity, increased risk of uterine rupture during labor, increased risk of miscarriage, premature delivery, and placental complications such as accretism[28,34].

On the other hand, surgery for myometrial reduction, which consists of the surgical removal of the affected myometrial tissues, is an alternative treatment option. This is a complex surgical procedure involving the removal of adenomyotic tissues, which is associated with an increased risk of intraoperative bleeding, as well as an increased chance of uterine rupture during subsequent pregnancy and intrauterine syncytia. There are no controlled studies evaluating the effect of this surgery on fertility, and it should therefore not be an approach for patients seeking fertility preservation[29].

Uterine artery embolization may be able to produce changes in the areas of adenomyosis with decreased vascularization of the JZ; however, this type of treatment is not indicated for infertile patients due to the risk of inducing premature ovarian failure, besides being able to interfere with endometrial receptivity[32].

The focal therapy with high-intensity focused ultrasound (HIFU) uses the thermal effect of the ultrasound beam, which causes coagulative necrosis within the target adenomyotic lesion. Thus, this method would be indicated for focal adenomyosis, being inadequate for the diffuse form. The advantage of this method would be a faster recovery time when compared to classical surgical techniques[35].

Conclusion

Adenomyosis has a negative impact on fertility with reduced pregnancy rate and increased abortion rate. The treatment of infertility associated with adenomyosis is still a very complex issue that needs more scientific support to define the best management and approach. So far there is no scientific evidence to indicate any surgical treatment for women with adenomyosis and desire for pregnancy or that are in infertility treatment. Surgery for adenomyosis, whether conservative or radical, is reserved for cases of symptomatic women (dysmenorrhea and abnormal uterine bleeding) with defined progeny.

Based on current data, the recommendations for the definition of the best treatment for adenomyosis in infertile women are based on weak evidence, and assisted reproductive techniques are an available resource in these cases. The literature shows us that the use of GnRh agonist before the IVF cycle can be beneficial, improving reproductive outcomes. However, further studies are still needed to answer the still existing doubts, define diagnostic criteria, and create protocols to approach adenomyosis.

Author's Contribution

AM Miranda proposed the theme developed and participated in the review and guidance. MC Magalhaes participated in the review and guidance. LB Viana participated in the bibliographic survey and the results of the article, carried out the introduction and conclusion of the article and sent the article. LB Lima participated in the results of the article and the bibliographic survey. SO Domingos carried out the production of references and methodology, and participated in the bibliographical survey and the production of the result of the article. LM Amaral produced the abstract of the article in question, as well as participated in the bibliographic survey and the production of the article's result. All authors conceptualized, discussed, read and approved the final version of the article.

Copyright

Copyright© 2023 Viana et al. This is na Open Access article distributed under the terms of the Creative Commons Attribution 4.0 International License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original article is properly cited.

References

1. Vercellini P, Bonfanti I, Berlanda N. Adenomyosis and infertility: Is there a causal link? Expert Rev Endocrinol Metab. 2019;14(6):365-7.
2. Younes G, Tulandi T. Effects of adenomyosis on in vitro fertilization treatment outcomes: A meta-analysis. Fertil Steril. 2017;108(3):483-90.
3. Garcia-Velasco JA. Is there a link between focal adenomyosis and infertility? Fertil Steril. 2020;114(6):1179.
4. Vercellini P, Consonni D, Barbara G, Buggio L, Frattaruolo MP, Somigliana E. Adenomyosis and reproductive performance after surgery for rectovaginal and colorectal endometriosis: a systematic review and meta-analysis. Reprod Biomed Online. 2014;28(6):704-13.
5. Juang CM, Chou P, Yen MS, Twu NF, Horng HC, Hsu WL. Adenomyosis and risk of preterm delivery. BJOG. 2007;114(2):165-9.
6. Khandeparkar MS, Jalkote S, Panpalia M, Nellore S, Mehta T, Ganesan K, et al. High-resolution magnetic resonance imaging in the detection of subtle nuances of uterine adenomyosis in infertility. Global Reproductive Health. 2018;3(3):1-8.
7. Vlahos NF, Theodoridis TD, Partsinevelos GA. Myomas and adenomyosis: Impact on reproductive outcome. Biomed Res Int. 2017;2017:1-14.
8. Kunz G, Beil D, Deininger H, Wildt L, Leyendecker G. The dynamics of rapid sperm transport through the female genital tract: Evidence from vaginal sonography of uterine peristalsis and hysterosalpingoscintigraphy. Hum Reprod. 1996;11(3):627-32.

9. Kido A, Togashi K, Nishino M, Miyake K, Koyama T, Fujimoto R, et al. Cine MR imaging of uterine peristalsis in patients with endometriosis. Eur Radiol. 2006;17(7):1813-9.

10. Piver P. Uterine Factors Limiting ART Coverage. J Gynecol Obstet Biol Reprod. 2005;34(7 Pt 2):5S30-3.

11. Ota H, Tanaka T. Stromal vascularization in the endometrium during adenomyosis. Microsc Res Tech. 2003;60(4):445-9.

12. Naftalin J, Hoo W, Pateman K, Mavrelos D, Holland T, Jurkovic D. How common is adenomyosis? A prospective study of prevalence using transvaginal ultrasound in a gynaecology clinic. Hum Reprod. 2012;27(12):3432-9.

13. Vannuccini S, Tosti C, Carmona F, Huang SJ, Chapron C, Guo S-W, et al. Pathogenesis of adenomyosis: An update on molecular mechanisms. Reprod Biomed Online. 2017;35(5):592-601.

14. Jiang Y, Jiang R, Cheng X, Zhang Q, Hu Y, Zhang H, et al. Decreased expression of NR4A nuclear receptors in adenomyosis impairs endometrial decidualization. Mol Hum Reprod. 2016;22(9):655-68.

15. Harada T, Khine YM, Kaponis A, Nikellis T, Decavalas G, Taniguchi F. The impact of adenomyosis on women's fertility. Obstet Gynecol Surv. 2016;71(9):557-68.

16. Tremellen KP, Russell P. The distribution of immune cells and macrophages in the endometrium of women with recurrent reproductive failure. II: Adenomyosis and macrophages. J Reprod Immunol. 2012;93(1):58-63.

17. Ishikawa M, Nakata T, Yaginuma Y, Nishiwaki K, Goishi K, Saitoh S. Expression of superoxide dismutase (SOD) in adenomyosis. Am J Obstet Gynecol. 1993;169(3):730-4.

18. Orazov MR, Radzinsky VE, Nosenko EN, Khamoshina MB, Dukhin AO, Lebedeva MG. Immune-inflammatory predictors of the pelvic pain syndrome associated with adenomyosis. Gynecol Endocrinol. 2017;33(Suppl 1):44-6.

19. Takahashi K, Nagata H, Kitao M. Clinical usefulness of determination of estradiol level in the menstrual blood for patients with endometriosis. Nihon Sanka Fujinka Gakkai Zasshi. 1989;41(11):1849-50.

20. Lessey BA, Palomino WA, Apparao KBC, Young SL, Lininger RA. Estrogen receptor-alpha (ER-alpha) and defects in uterine receptivity in women. Reprod Biol Endocrinol. 2006;4(Suppl 1):S9.

21. Bourdon M, Santulli P, Oliveira J, Marcellin L, Maignien C, Melka L, et al. Focal adenomyosis is associated with primary infertility. Fertil Steril. 2020;114(6):1271-7.

22. Buggio L, Monti E, Gattei U, Dridi D, Vercellini P. Adenomyosis: Fertility and obstetric outcome. A comprehensive literature review. Minerva Ginecol. 2018;70(3):295-302.

23. Szubert M, Koziróg E, Olszak O, Krygier-Kurz K, Kazmierczak J, Wilczynski J. Adenomyosis and infertility—review of medical and surgical approaches. Int J Environ Res Public Health. 2021;18(3):1235.

24. Chiang CH, Chang MY, Shiau CS, Hou HC, Hsieh TT, Soong YK. Effect of a sonographically diffusely enlarged uterus without distinct uterine masses on the outcome of in vitro fertilization-embryo transfer. J Assist Reprod Genet. 1999;16(7):369-72.

25. Mijatovic V, Florijn E, Halim N, Schats R, Hompes P. Adenomyosis has no adverse effects on IVF/ICSI outcomes in women with endometriosis treated with long-term pituitary down-regulation before IVF/ICSI. Eur J Obstet Gynecol Reprod Biol. 2010;151(1):62-5.

26. Thalluri V, Tremellen KP. Ultrasound diagnosed adenomyosis has a negative impact on successful implantation following GnRH antagonist IVF treatment. Hum Reprod. 2012;27(12):3487-92.

27. Martínez-Conejero JA, Morgan M, Montesinos M, Fortuño S, Meseguer M, Simón C, et al. Adenomyosis does not affect implantation, but is associated with miscarriage in patients undergoing oocyte donation. Fertil Steril. 2011;96(4):943-50.

28. Huang BS, Seow KM, Tsui KH, Huang CY, Lu YF, Wang PH. Fertility outcome of infertile women with adenomyosis treated with the combination of a conservative microsurgical technique and GnRH agonist: Long-term follow-up in a series of nine patients. Taiwan J Obstet Gynecol. 2012;51(2):212-6.

29. Won S, Hwang JY, Lee N, Kim M, Kim MK, Kim ML, et al. Anti-müllerian hormone level may predict successful pregnancy after adenomyomectomy in patients with infertility due to adenomyosis. Medicine. 2021;100(21):1-6.

30. Niu Z, Chen Q, Sun Y, Feng Y. Long-term pituitary downregulation before frozen embryo transfer could improve pregnancy outcomes in women with adenomyosis. Gynecol Endocrinol. 2013;29(12):1026-30.

31. Park CW, Choi MH, Yang KM, Song IO. Pregnancy rate in women with adenomyosis undergoing fresh or frozen embryo transfer cycles following gonadotropin-releasing hormone agonist treatment. Clin Exp Reprod Med. 2016;43(3):169-73.

32. Donadio N, Donadio NF, Dotore A, Silva FF, Ribeiro PA, Aoki T. Aplicação de dispositivo intra-uterino Liberador de levonorgestrel, previamente a ciclos de fertilização in vitro, nas portadoras de adenomiose. Rev Bras Ginecol Obstet. 2006;28(8):473-8.

33. Osuga Y, Fujimoto-Okabe H, Hagino A. Evaluation of the efficacy and safety of dienogest in the treatment of painful symptoms in patients with adenomyosis: a randomized, double-blind, Multicenter, placebo-controlled study. Fertil Steril. 2017;108(4):673-8.

34. Soave I, Wenger J-M, Pluchino N, Marci R. Treatment options and reproductive outcome for adenomyosis-associated infertility. Curr Med Res Opin. 2017;34(5):839-49.

35. Zhang L, Rao F, Setzen R. High intensity focused ultrasound for the treatment of adenomyosis: Selection criteria, efficacy, safety and fertility. Acta Obstet Gynecol Scand. 2017;96(6):707-14.

This is an open access article distributed under the terms of the Creative Commons Attribution License.