Review Article

Infertility and Adenomyosis

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Abstract Adenomyosis is a benign disease associated with menstrual irregularities, pain, and infertility, primarily affecting women belonging to the reproductive age group. The advent of superior imaging modalities have increased the diagnosis of this condition. Adenomyosis has been shown to be correlated with a negative impact on fertility. Treatment options for this condition are mainly medical and surgical.

Keywords: Adenomyosis, Infertility, Surgery

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Submission: 10–09–2023, **Revised:** 13–09–2023, **Accepted:** 14–09–2023, **Published:** 30–September–2023

INTRODUCTION

Adenomyosis or endometriosis genitalis interna is a condition in which epithelial cells of the endometrium and fibroblasts from stroma invade the uterine myometrium consequently resulting in hyperplasia, hypertrophy, and fibrosis of the myometrium.

Historically, the diagnosis of adenomyosis was made on the histopathology report of uterine specimen, for hysterectomy performed in older woman.[1] However, presently adenomyosis has been demonstrated in younger females belonging to reproductive age group presenting with dysmenorrhea, abnormal uterine bleeding, dyspareunia, pelvic pain, or infertility. In one third of cases, adenomyosis has been an incidental diagnosis in asymptomatic patients.[2] Additionally, adenomyosis coexisting with endometriosis and uterine fibroids has also been demonstrated.[3]

Ultrasound can be used to visualize adenomyosis uteri in 20.9% of cases.[4] Around 10 to 35% of histopathologic findings of posthysterectomy uterus specimen reveal adenomyosis.[5] As per a study on infertile women, the prevalence of adenomyosis is 22% in women younger than 40 years age and 24.4% in women older than 40 years of age. Adenomyosis prevalence was calculated to be 38.2% in cases of recurrent pregnancy loss and 20 to 25% in women undergoing treatment via assisted reproductive technologies (ARTs) for infertility.[6] Around 20 to 80% of women having adenomyosis have associated endometriosis also.[7]

ASSOCIATION WITH INFERTILITY

Many theories have been proposed to explain how adenomyosis can lead to infertility. Patients suffering from adenomyosis have been shown to exhibit abnormal utero-tubal transport owing to the anatomical distortion of the uterine cavity by the pathology. Additionally, adenomyomas can also obstruct the tubal ostia thereby impeding migration of sperms as well as the transport of the embryo, resulting in infertility.

Access this article online	
Quick Response Code:	Website: www.fertilityscienceresearch.org
	DOI: 10.4103/fsr.fsr_33_23

How to cite this article: Pinkee S, Vidushi S. Infertility and Adenomyosis. Fertil Sci Res 2023;10:139-44.

Hricak *et al.*[8] was the first to elucidate the functional uterine zone, which signifies the junction between the endometrium and the inner myometrium. Based on magnetic resonance imaging (MRI) it is divided in to three distinct layers—a high signal intensity signifying the endometrial stripe, an inner low signal intensity in proximity to the basal endometrium correlating to the junctional zone (JZ) or subendometrial layer, and an outer medium signal intensity denoting the subserosal zone or outer myometrium. In patients affected by adenomyosis, invagination of the endometrial glands and stroma causes alteration of JZ and inner myometrium leading to the development of dysfunctional hyperperistalsis and increased intrauterine pressure. This in turn negatively impacts sperm transport and fertility in these patients. Increased uterine JZ activity just prior to embryonic transfer in *in vitro* fertilization (IVF) is also associated with a reduced pregnancy rate and increased frequency of ectopic pregnancy.[9] A JZ >7 mm is associated with higher implantation failure.[10] Studies have also proposed a positive relationship between spontaneous abortion and JZ function.[11]

A plethora of molecular alterations have been seen in the endometrium of infertile women with adenomyosis which have caused development of altered receptivity.[12] Dysfunctional expression of mRNA and aromatase cytochrome P450 protein have been observed in the endometrium of women with adenomyosis.[13] There is evidence of increased inflammatory markers such as tumor necrosis factor alpha (TNF-α) and interleukin-1 (IL-1) along with reactive oxygen species produced by macrophages which are toxic to embryos.[14] Additionally, an abnormally high level of free radicals present in women with adenomyosis has detrimental effects on sperm transport, implantation, and decidualization.[15]

Dysfunctional implantation has been attributed to a reduced expression of implantation markers like leukemia inhibitory factor, to a lack of expression of adhesion molecules such as integrin β-3, osteopontin, and to the altered function of the gene for embryonic development *HOXA10*.[16]

DIAGNOSIS

Ultrasound and MRI are common modalities used for the diagnosis of adenomyosis.

Ultrasound

Adenomyosis can be either diffuse or focal. Focal adenomyosis presents as adenomyoma, pseudo-widening, and hemorrhagic cysts.

Various criteria have been used to define adenomyosis on ultrasound. Van den Bosch *et al.*[17] suggested that while examining and describing a uterus with adenomyosis, the following factors should be assessed:

- Presence of adenomyosis appears as an enlarged globular uterus which has irregular thickening of the myometrium, presence of myometrial cysts, echogenic subendometrial lines and bumps, hyperechogenic areas, an irregular or broken JZ, and vascularity of the lesion on color Doppler.[18]
- Description of the lesions—focal or diffuse mixed
- Location of disease, i.e., anterior, posterior, left lateral, right lateral, fundal
- Myometrial layer involvement (JZ, myometrium, serosa)
- Presence or absence of intralesional cysts
- Lesion size
- Extent of uterine volume affected

This system although having a few limitations can aid in standardizing the ultrasound description of adenomyosis.

Magnetic Resonance Imaging

MRI has utility in identifying variations in JZ and to exclude other diseases. Higher diagnostic yield of adenomyosis is obtained when it is performed in the secretory phase of the menstrual cycle. It appears as a poorly demarcated area of low signal intensity on T2-weighted images. The JZ is seen well in T2-weighted images, which is characteristically increased in thickness in this pathology.[19] A JZ thickness of >12 mm makes the diagnosis of adenomyosis highly probable.[20]

EFFECT ON REPRODUCTIVE OUTCOMES

There is limited data on the effect of adenomyosis on pregnancy, but several studies have described the impact of it on women undergoing infertility treatment.

Vercellini *et al.* in a meta-analysis reported a higher miscarriage rate in women with adenomyosis (31%) compared to those without the condition (14.1%).[21] Another study found that the presence of definite morphological features of adenomyosis on ultrasound was associated with poor reproductive outcomes, including decreased clinical pregnancy rates. Clinical pregnancy rates decreased from 42.7% in women without it, to 22.9% in women with four ultrasound features and 13.0% in women with all the ultrasound features of adenomyosis.[22]

Furthermore, a meta-analysis[23] on IVF treatment outcomes in adenomyosis showed reduced rates of implantation, clinical pregnancy per cycle, clinical pregnancy per embryo transfer, ongoing pregnancy, and live-birth rate. The study also suggested that pre-IVF treatment with a gonadotropin-releasing hormone analogue (GnRHa) may be beneficial for pregnancy. Similar results was observed in women with endometriosis and adenomyosis.[24]

Zang *et al.*[25] studied the effect of adenomyosis on assisted reproductive techniques. They found a significantly higher early abortion rate in the adenomyosis group compared to the control group (13.3 vs 5.6%, respectively; $P = 0.012$).

Bourdon *et al.*[26] examined the association of adenomyosis with infertility and found a clear association between focal adenomyosis and primary infertility. They also observed that a majority of women with focal adenomyosis had associated endometriosis, supporting the common presence of these two conditions.

Overall, these studies suggest that adenomyosis can have a detrimental effect on reproductive outcomes, including decreased pregnancy rates and increased risk of miscarriage. It also highlights the potential association between adenomyosis and endometriosis.

TREATMENT

Medical Treatment

Various drugs have been utilized in the management of symptomatic treatment of adenomyosis and associated infertility.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used as a first-line treatment for pain in women with adenomyosis. However, NSAIDs may have a negative effect on fertility by delaying the rupture of ovarian follicles. Combined oral contraceptive pills are used to treat symptoms such as dysmenorrhea and abnormal uterine bleeding in patients with adenomyosis. Limited data are available on the impact of oral contraceptive pills on subsequent fertility improvement. Dienogest is primarily used to regress adenomyosis due to its hypoestrogenic, hypergestagenic, and anti-inflammatory properties. Long-term dienogest therapy has been found to be suitable for adenomyosis treatment by Neriishi *et al.*[27] However, it may be associated with side effects such as irregular spotting or bleeding.[28]

The levonorgestrel-releasing intrauterine system (LNG-IUS) can also be used for infertility treatment in women with adenomyosis. Pretreatment with LNG-IUS has been shown to enhance ongoing pregnancy rates, implantation rates, and clinical pregnancy rates in women undergoing IVF in a study by Liang *et al.*[29] They observed higher pregnancy rates (41.8 vs 29.5%), higher implantation rates (32.1 vs 22.1%), and higher clinical pregnancy rates (44 vs 33.5%) in the LNG-IUS group as compared to the control group.

GnRHa with add-back therapy are employed to treat adenomyosis. GnRHa initially stimulate the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), leading to an increase in estrogen secretion. However, continuous secretion results in downregulation of FSH and LH receptors, causing a decrease in estrogen secretion. GnRHa treatment has been shown to reduce the size of adenomyotic lesions[30,31] and have a positive effect on endometrial implantation markers.[32]

Younes *et al.*[23] in a meta- analysis have observed that pretreatment with GnRHa is rewarding in patients with adenomyosis undergoing IVF. A similar result was seen in IVF with frozen embryo transfer.[33] Wu *et al.*[34] came to the conclusion that frozen embryo transfer following pretreatment with GnRHa was beneficial in IVF/intracytoplasmic sperm injection cycle, and required a lower dose of gonadotrophin and with a shorter duration of stimulation than fresh embryo transfer combined with a long or ultra-long GnRHa protocol.

Hou *et al.*[35] in a study observed that in patients with adenomyosis, clinical pregnancy rate, implantation rate, and live birth rate were higher in the ultra-long GnRH agonist therapy compared with long GnRH agonist therapy.

Lan *et al.*[36] in their study observed that miscarriage rate in women receiving the ultra-long GnRHa protocol was less as compared to those receiving the long GnRHa protocol (12.0 vs 26.5%); however, no statistical differences were seen in the rates of biochemical pregnancy, implantation, clinical pregnancy, and live birth between the two groups. The pregnancy outcomes were also analyzed according to the adenomyosis type. Patients with diffuse adenomyosis who received ultra-long GnRHa protocol had a higher clinical pregnancy rate and live birth rate in women when compared to those receiving the long GnRHa protocol (55.3 vs 37.9%; 43.4 vs 25.9%, respectively). However, this difference was not seen in women with focal

adenomyosis. Treatment with ultra-long GnRH agonist protocol had a better reproductive outcome when compared to treatment with long GnRH agonist protocol in women with adenomyosis, especially in women with diffuse adenomyosis.

On contrary, Chen *et al.*[37] in their study, observed that pretreatment with GnRH agonist was not beneficial in women undergoing IVF/ICSI treatment with fresh embryo transfer.

Cozzolino *et al.*[38] in their study observed that surgical treatment improves natural conception in women with adenomyosis (in two studies), and medical treatment with GnRHa does not increase pregnancy in IVF cycles (in three studies).

A recent case report[39] has demonstrated the beneficial outcomes of linzagolix, a new oral GnRH antagonist, in reducing uterine volume, decreasing uterine bleeding and pain, and improving the quality of life in a patient with severe adenomyosis.

Overall, medication options for adenomyosis aim to manage symptoms and improve fertility outcomes, but more research is needed to understand their long-term effects and optimize treatment approaches.

CYTOREDUCTIVE SURGERY

Since the first procedure to treat adenomyosis surgically by Hyams,[40] various surgical approaches have been added to the arsenal of treatment.

Surgical treatment options for adenomyosis include laparoscopic or open procedures, with the goal of either partially or completely removing the adenomyotic tissue. Partial reduction can be achieved through techniques such as wedge resection or a transverse H incision on the uterus,[41] followed by the removal of the adenomyotic tissue using diathermy or a cold knife. The uterine walls are then sutured using various methods such as U-sutures, figure-of-eight sutures, or interrupted sutures. Closure of the uterine wall can be done by overlapping the seromuscular layer in a double or triple flap layers method. The complete triple flap technique is effective for both diffuse uterine adenomyosis and nodular adenomyosis, and it helps reduce[42] the risk of uterine rupture during pregnancy.

Systematic reviews have been conducted on uterine surgery for adenomyosis. One review[43] reported that complete excision resulted in an 82.0% reduction in dysmenorrhea and a 68.8% reduction in menorrhagia, with a pregnancy rate of 60.5%. Partial excision led to an 81.8% reduction in dysmenorrhea and a 50.0% decrease in menorrhagia, with a pregnancy rate of 46.9%. Tan *et al.*[44] analyzed the role of surgery in infertile women with focal and diffuse adenomyosis and found that the mean pregnancy rates were 52.7% for focal adenomyosis and 34.1% for diffuse adenomyosis. No difference was noted in the pregnancy rate between natural or IVF conception with or without gonadotropin-releasing hormone agonist pre-treatment. Patients with focal adenomyosis had better pregnancy outcome after conservative surgery than those with diffuse adenomyosis. Diffuse adenomyosis was associated with an increased risk of uterine rupture and preterm birth.

A study done by Kishi *et al.*[45] factors can impact fertility outcomes following uterine surgery for adenomyosis, including a history of IVF treatments, the presence of posterior wall adenomyosis, and the age of the patient. Younger women who had previous IVF failure had a higher chance of successful pregnancy following surgery.[45]

Wang *et al.*[46] studied the role of surgical intervention in the management of subfertile women with symptomatic extensive uterine adenomyosis. They observed that surgical intervention, either alone or in combination with GnRH agonist therapy, was found to be more effective in managing symptoms and improving pregnancy and delivery rates compared to GnRH agonist therapy alone.

One major drawback of uterine surgery for adenomyosis is the increased risk of uterine rupture during pregnancy, which is higher compared to pregnancies after myomectomy[47,48] (>1.0 vs 0.26%).

Otsubo *et al.*[49] observed that maintaining an adequate thickness of the uterine wall, preferably between 9 and 15 mm, is important for conception and the prevention of uterine rupture.

Osada *et al.*[50] reviewed surgical methods available for the treatment of adenomyosis. They inferred that it is feasible to treat focal adenomyosis lesion laparoscopically. However, for diffuse adenomyosis, laparotomy or laparoscopically assisted laparotomy is suggested as a better alternative. Laparotomy is safer than laparoscopy as in open surgery the entire lesion can be completely excised to prevent the recurrence. Additionally, good

reconstruction of the myometrial circumvents uterine rupture during pregnancy.

OTHER ALTERNATIVES

High-intensity focused ultrasound (HIFU) is a novel noninvasive modality that can be used for the treatment of adenomyosis. A study showed that HIFU in combination with GnRHa[51] for the treatment of adenomyosis can effectively decrease the symptoms as well as reduce the size of lesions as compared to used HIFU alone.

Radiofrequency ablation[52] is also a newly introduced treatment modality for adenomyosis. It is also minimal invasive method that can be used for short-term pain relief in symptomatic adenomyosis patients. Further studies are needed to evaluate its impact on other factors such as irregular bleeding, fertility, pregnancy outcome, and quality of life.

CONCLUSION

Adenomyosis is a benign pathology of uterus that is emerging as a cause of infertility. It is associated with decreased implantation, pregnancy loss, and preterm birth. Treatment of infertility in these patients remains a challenge for the clinicians with the present modalities. Conservative medical treatment along with fertility sparing surgery done alone or in combination have been used to improve fertility outcomes for the patients. Treatment should be appropriately individualized depending upon age, duration of infertility, previous failed treatment, and ovum preservation. Further research is still warranted to explore new, more effective, safe, and less invasive treatment of women with infertility due to adenomyosis.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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