

Review

Pathogenesis and treatment status of adenomyosis complicated with infertility

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Highlights:

The treatment options for patients of AD with infertility should follow the principle of individual treatment and choose the most appropriate method based on the specific conditions of the hospital.



Adenomyosis  **Infertility**

Abstract

Adenomyosis (AD) refers to the endometrium (including glands and stroma) into myometrium growth of pathological changes, with the delay of women's childbearing age, the patients with AD-associated infertility increased significantly. Although scholars disagreed about the effect of AD on infertility, more and more evidence showed that AD was closely related to the structural and functional defects of the eutopic endometrium and myometrial junctional zone (MJZ), which may lead to embryo implantation failure and infertility. With the rapid development of imaging technology, the accuracy of diagnose AD has been enhanced, more and more infertility patients were diagnosed with AD. At the same time, a series of pathogenic hypothesis have been proposed to explain the relationship between AD. In addition, AD may influence the patient's reproductive function by affecting sperm transport, embryo implantation, altering uterine peristalsis, influencing the structure and function of endometrium, and changing the intrauterine environment. At present, the treatment of AD-associated infertility is similar to the treatment of AD. The commonly used treatment methods include drug therapy, conservative operative treatment, drug combination surgery, and Chinese medicine treatment and so on. The clinical and experimental studies of AD complicated with infertility and its possible pathogenesis and treatment in recent years are reviewed in this article.

Keywords: Adenomyosis; Infertility; Pathogenesis; Treatment; Endometrium

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Abbreviation

AD, Adenomyosis; MJZ, Myometrial junctional zone; MMP, matrix metalloproteinases; HOXA10, homeobox A10; LIF, Leukocyte suppressor factor; GnRH-a, Gonadotropin-releasing hormone agonist.

Competing interests:

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Introduction

Adenomyosis (AD) refers to the endometrium (including glands and stroma) into myometrium growth of pathological changes [1]. The clinical manifestations of this disease were more progressive dysmenorrhea, menstrual flow increased, menstrual extension, increased uterine uniformity (spherical) or limited nodular uplift. AD is a common disease in women at reproductive age, especially among women aged 30 to 50 [2]. With the delay of women's childbearing age, the patients with AD-associated infertility increased significantly. According to the pathological findings of hysterectomy, the incidence of AD was from 8% to 27% [3].

The scholars disagreed about the effect of AD on infertility, some scholars believed that AD was not common in subfertility women, while other scholars believed that AD played a key role in infertility [4]. With the rapid development of imaging technology, especially the application of high resolution ultrasonography and magnetic resonance imaging, the accuracy of diagnose AD has been enhanced, more and more infertility patients were diagnosed with AD [5]. At the same time, a series of pathogenic hypothesis have been proposed to explain the relationship between AD and infertility, and prompted people to continuously explore new therapeutic methods. In the last few decades, a variety of methods such as medicaments, operation has been trying for the treatment of AD combined infertility, and obtained a certain effect, but so far, the world has not yet agreed on the treatment of the disease. This paper reviews the clinical and experimental studies about the possible pathogenesis and treatment of AD complicated with infertility in recent years.

The effect of AD on infertility and its possible pathogenesis

So far, the relationship between AD and infertility has not been clear. More and more evidence showed that AD was closely related to the structural and functional defects of the ectopic endometrium and myometrial junctional zone (MJZ), which may lead to embryo implantation failure and infertility. Piver *et al.* suggested that AD may influence the patient's reproductive function by affecting sperm transport, embryo implantation, and changing the intrauterine environment [6]. According to the results of existing studies, the pathophysiological mechanism of AD affecting female infertility may have the following aspects.

Influence MJZ

In 1984, Birnholz first proposed that the presence of an obvious peristaltic wave in the myometrium by abdominal ultrasound, which originated in MJZ. During the follicular phase or preovulation, the uterus moved toward the cervix, until the ovulation period increased its amplitude and frequency. This peristaltic wave played an important role in the process of reproduction: such as endometrial transformation, menstruation, sperm transport and implantation [7]. Mehaseb *et al.* studied the fine structure of the normal uterus and AD uterus, found that there were some differences, that was, AD patients' MJZ cells and nuclei increased, the structure of nucleus and mitochondria was unusual, there were large amounts of myelin small bodies and so on [8]. Abnormal fine structure may disturb the Ca cycle of normal muscle cells, thus losing the normal contraction rhythm, affecting the sperm rapidly and directly into the uterine cavity, the uterus fallopian tube transport capacity gradually decreased, intervening sperm-egg combination and fertilized egg implantation, eventually leading to infertility.

Affect the structure of uterine cavity

Abnormal uterine anatomy caused by AD may be an important cause of infertility. Severe AD or uterine adenomyoma increased the size of the uterus and the distribution of lesions, leading to a decline in the pregnancy rate of natural insemination or assisted reproduction. One study showed that uterine adenomyoma changed the normal morphology of uterine cavity, may block the opening of the fallopian tube, interfered with the sperm transport and embryo implantation, or uterus volume increased after extrusion fallopian tubes and ovaries, thus affecting fertilization [9].

Alter uterine peristalsis

One effect of AD on fertility may be the rapid, sustained, and accurate delivery of sperm by affecting MJZ. The MJZ structure of AD was abnormal and the contraction of MJZ muscle layer with disorder, which caused the disorder of rhythm, amplitude and direction, and may hinder the transportation of sperm to oviduct and the implantation of fertilized egg. AD patients due to the basal layer of the intima and interstitial invasion to the myometrium, destructing the ring structure of the endometrial muscle, making uterine muscle cell proliferation and disorder, leading to increased bureaucratic pressure and uterine motility disorders. Finally, the rapid and persistent sperm direct transport mechanism of the uterus was affected, and the normal planting process of the embryo was disturbed. Kissler *et al.* showed that radionuclides in women of childbearing age were transported

unidirectionally to the side of dominant follicles, while 70% of radionuclides in women with diffuse AD-associated infertility still remain in the uterine cavity, 22% was transported to the opposite side, only 8% on the same side [10].

Influence the structure and function of endometrium

Different vascular distribution in the endometrium of patients with AD and normal female, a third of abnormal vascularization was performed after the hysterectomy of patients with AD: irregular vascular distribution, the blood vessels were thick and expandable with a network distribution [11]. The study showed that compared with women of normal fertility, there was a significant increase in uterine endometrial angiogenesis in patients with AD, and the total surface area of microvessels was 11.6 times of that of the control group [12]. Li *et al.* found that elevated levels of matrix metalloproteinases (MMP)-2 and MMP-9 may be an important factor in the development of AD, which could promote the angiogenesis of endometrial tissue infiltrating into the myometrium and lesion [13]. RCAS1 is a molecule that inhibits natural killer cells and the proliferation and activation of T lymphocytes. Results showed that the concentration of RCAS1 in serum was the highest in the secretory period and the lowest in the proliferative phase, while the RCAS1 concentration in the patients with AD was almost constant, suggesting that abnormal expression of RCAS1 may affect the endometrium decidualization of patients with AD, eventually leading to infertility [14]. In addition, inflammatory factors such as interleukin (IL), -6, IL-8 and IL-10 secreted by the endometrium of AD patients were significantly increased, which may also affect the function of endometrium and conception [15-17].

Abnormal endometrial free radicals

Low concentration of oxygen free radicals was essential for early embryonic development, while abnormal free radical concentration in the endometrium of AD may be one of the causes of infertility. Enzymes in the body (such as xanthine oxidase, superoxide dismutase, glutathione peroxidase and NO synthase) can generate and eliminate free radicals, thereby making free radicals at a suitable concentration and maintaining the dynamic balance. The enzymes of NOS, xanthine oxidase, superoxide dismutase and H₂O₂ in endometrium of AD and endometriosis patients were over expressed and not fluctuated with menstrual cycle [18]. Due to breaking of the balance between reactive oxygen and antioxidants, excessive oxygen free radicals were produced, damaging the fertilized

eggs and inhibiting embryonic development and pregnancy [19].

Affect the embryo implantation

A large number of cell adhesion molecules expressed in the endometrium were essential for the successful interaction between the embryo and the endometrium. These “implant markers” were often used as indicators of endometrial receptivity in clinical practice. The abnormal expression of homeobox A10 (HOXA10) may be an important factor affecting the embryo implantation in patients with AD. HOXA10 was one of the important implantation regulatory genes. The expression of HOXA10 in vivo was regulated by estrogen and progesterone, which was expressed periodically in the endometrium, highest in the window phase and decreased in endometriosis and other abnormalities. The expression of HOXA10 gene in patients with AD was significantly reduced [20], suggesting that the attenuation of HOXA10 may be one of the reasons for the decline of embryo planting rate in patients with AD.

Leukocyte suppressor factor (LIF) was also an important cytokine in the successful implantation of fertilized eggs. Studies have shown that the expression of LIF decreased significantly in the endometrium of AD patients during the middle secretory phase, and the concentration of LIF in the uterine irrigating fluid of AD patients complicated with infertility was significantly lower than that in women with normal reproductive function [21]. Therefore, the decreased expression of LIF receptors in the endometrium during embryonic implantation may also be one of the molecular mechanisms leading to low rate of implantation in patients with AD.

Treatment of AD complicated with infertility

In recent years, a variety of therapies have been used in the treatment of AD combined with infertility. However, there was no consensus on the treatment of AD with infertility worldwide. At present, the treatment of AD-associated infertility in China and abroad is similar to the treatment of AD. The commonly used treatment methods include drug therapy, conservative operative treatment, drug combination surgery, and Chinese medicine treatment and so on.

Drug treatment

Gonadotropin-releasing hormone agonist (GnRH-a) GnRH-a is one of the most widely accepted and widely accepted treatment methods, a number of case studies have reported that patients

treated with this drug were successful in pregnancy and delivery. GnRH-a is a kind of long-term gonadotropin-releasing hormone agonist that acts on the pituitary gland and inhibits ovarian function by regulating the pituitary gonadotropin, eventually leading to sustained low estrogen level in the body. The low estrogen level caused by GnRH-a could absorb myometrial lesions, made uterine soft, also had immunomodulatory effect and reduced the concentration of immune factors in ascites (including tumor necrosis factor and interleukin), significantly improved the peritoneal and local inflammatory response, reduced the pelvic pain [22]. The study showed that after the treatment of GnRH-a, the expression of endometrial aromatic enzyme cytochrome P450 could be reduced and the synthesis of estrogen was inhibited in patients with AD and endometriosis [23]. The study found that GnRH-a significantly reduced the inflammatory response and angiogenesis caused by AD, and increased necrotic tissue [24]. GnRH-a could also improve the tolerance of endometrium and increase the implantation rate of embryo transplantation [25].

Danazol Danazol mainly by blocking the synthesis and release of gonadotropin, direct inhibition of ovarian steroid synthesis, combined with endometrial progesterone and androgen receptors, inhibition of endometrial cell proliferation, in order to achieve the purpose of treatment of AD [26]. A case study showed that the cumulative pregnancy rate of patients with AD was 41% after the treatment with Danazol [27]. However, recent studies have found that the drug could cause high-density lipoprotein levels, long-term use could cause the risk of atherosclerotic heart disease.

Gestrinone Gestrinone has the effect of anti-progesterone, anti-estrogen and anti-gonadal, it directly and indirectly increases the level of free testosterone, reduces sex hormone binding globulin levels and serum estradiol levels, can cause low estrogen status in the body, plays a drug temporarily cast the state to achieve therapeutic purposes. Studies have found that Gestrinone in the treatment of dysmenorrhea with uterine AD compared with GnRH-a were statistically different, and Gestrinone could make liver damage, especially taking medication within 1 month, often drug withdrawal because of abnormal liver function, and 30%~50% patients with recurrence after 6 months of stopping drug [28-29].

Other drugs In recent years, there were some reports on the treatment of AD with the use of Dienogest and Letrozole, as well as the epoxy synthase inhibitor, matrix metalloproteinase inhibitor and vascular growth inhibitor [30-32]. These drugs could theoretically be the new drugs for the treatment of

AD, but there is no evidence of a large sample of evidence-based medicine.

Conservative surgical treatment

Compared with GnRH-a, the improvement of reproductive function after conservative surgery was more significant [33]. But the surgical intervention was not the first choice for the treatment of AD with infertility, the most important reason is difficult to grasp the surgical indications, the scope of surgical resection could not be clearly defined, intraoperative suture was difficult, high technical requirements of performer was needed. In addition, conservative surgery could not completely remove the lesion of AD, and postoperative may lead to some sequelae, such as pelvic adhesions, uterine volume reduction and endometrial damage, which may affect the patient's pregnancy. Osada *et al.* showed that 26 patients with AD who had fertility requirements, in which 16 patients had successful pregnancy and 14 patients had a healthy neonatal term without uterine rupture [34].

Conservative surgery combined with drug treatment

Due to the transient effect of drug treatment of AD-related diseases and surgery treatment has an efficiency of only 50%, some scholars have suggested that conservative treatment + drug (GnRH-a) combined treatment of AD with infertility. Comparative studies have been conducted on the effect of surgery with GnRH-a treatment and GnRH-a alone treatment, the live birth rate of the two groups were 32.1%, 8%, the probability of live birth after combined treatment was 3.91 times of that using GnRH-a alone [33]. The study group analyzed the result of combined treatment and single conservative surgery in the other study, found that the combined therapy were more effectively control symptoms than conservative treatment, reduce the recurrence rate of symptoms, but the clinical pregnancy rate and delivery rate showed no statistical difference [35].

Chinese medicine treatment

There is no "uterine adenomyosis" in Chinese traditional medicine, and the uterine AD is mainly characterized by progressive and secondary dysmenorrhea and infertility. Lu *et al.* studied the effect of acupuncture and moxibustion combined with modified Siwu decoction on the treatment of AD [36]. Results compared with before treatment, the menstrual flow reduced, uterine length and uterine volume decreased in the two groups after treatment for 3 months and 6 months, the differences were statistically significant ($P < 0.05$). Chinese

traditional medicine scholars have developed a variety of treatment schemes, but there is no universally accepted effective plan.

Conclusion

AD is a common gynecological disease, and its influence on infertility is receiving more and more attention. Up to now, the pathogenesis of AD and the mechanisms that leading to infertility are not well been understand, there is also the lack of an optimal treatment. The treatment options for patients of AD with infertility should follow the principle of individual treatment and choose the most appropriate method based on the specific conditions of the hospital. With the further development of AD basic research and the gradual release of related pathogenesis, the treatment of AD tends to be more diversified, which will bring more hope to patients of AD with infertility.

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