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ADENOMYOSIS AND ITS IMPACT OF FEMALE INFERTILITY

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1. ABSTRACT

Introduction: The aim of this review is to explore the relationship between adenomyosis and infertility. The issue of adenomyosis and infertility is the subject of numerous scientific studies due to the mechanisms that may establish a correlation between them. These mechanisms present a dilemma for many researchers, and efforts to address it lead to increasingly innovative solutions for treating infertility and improving the reproductive health of women diagnosed with adenomyosis.

Material and methods: We have gathered the available materials and scientific reports, analyzing and summarizing them in a single study. An English-language literature review was conducted. We analysed studies from PubMed up to October 2024 regarding the correlation between adenomyosis and infertility.

Aim of study: We aimed to summarize the studies conducted so far by analyzing the available scientific reports to answer the question about adenomyosis correlation in infertility and understand it.

Conclusion: The article examines the relationship between adenomyosis and infertility, emphasizing its negative impact on the reproductive potential of women of reproductive age. Adenomyosis reduces pregnancy rates, increases the risk of miscarriages, and hinders embryo implantation, particularly in patients undergoing assisted reproductive techniques. Long protocols with GnRH analogs can improve treatment outcomes in both medical procedures and natural conception attempts. Surgical treatment may enhance fertility but carries risks of complications, and the effectiveness of surgery remains a topic of debate. Accurate diagnosis, appropriate therapy, and improved prenatal care for patients with adenomyosis are essential. Further research, including randomized controlled trials (RCTs), is needed to better understand the impact of adenomyosis on fertility and to develop effective treatment methods.

Keywords: adenomyosis, infertility, fertility, reproductive outcome, treatment.

2. INTRODUCTION

2.1. ADENOMYOSIS

Adenomyosis has been characterized as a benign uterine condition in which foci of heterotopic endometrial glands and stroma infiltrate the myometrium. This leads to uterine enlargement as well as abnormal uterine bleeding [1,2]. The majority of adenomyosis cases are observed in women in their fourth or fifth decade of life, although 5% to 25% of cases occur in younger women [3]. Adenomyosis often coexists with other conditions, such as leiomyomas and endometriosis, which complicates diagnosis [1, 4, 5]. Symptoms of adenomyosis include chronic pelvic pain, dysmenorrhea, heavy menstrual bleeding, intermenstrual bleeding, dyspareunia, and infertility [6]. Additionally, adenomyosis is associated with an increased risk of anxiety, depression, and psychosocial stress [7]. Common risk factors for adenomyosis include a high number of deliveries, spontaneous or induced miscarriages, age over 40, previous uterine surgeries or cesarean sections, and endometriosis. Recently, there has been an increase in diagnoses of adenomyosis among women with confirmed infertility [4, 8]. Moreover, adenomyosis has been shown to significantly impact the outcomes of assisted reproductive technologies [9]. The precise etiology of this condition has not yet been fully elucidated.

Several theories have been proposed, the most common being that adenomyosis results from the invagination of the basal endometrium into the uterine muscle. Another theory suggests it may arise from metaplasia of displaced Müllerian duct remnants or differentiation of stem cells [10].

2.2. THE IMPACT OF ADENOMYOSIS ON FERTILITY

The exact mechanism leading to infertility in women with adenomyosis remains not fully understood. The relationship between adenomyosis and female fertility is highly variable, as the clinical presentation can differ in terms of size, type, location, and severity of the lesions. Additionally, the presence of other conditions, such as leiomyomas (35% – 55%) or endometriosis (6% – 20%), can significantly impact the ability of women with adenomyosis to conceive [11, 12, 13]. A considerable number of recent studies on the effects of adenomyosis in women undergoing assisted reproductive technologies (ART) have revealed its negative impact on implantation and pregnancy rates during ART cycles [14, 15, 16, 17]. Various biological mechanisms may contribute to this outcome, including disruption of the normal structure and function of the myometrium [18], impaired uterine peristalsis and sperm transport [19], increased levels of reactive oxygen species [20], local hyperestrogenism [21, 22], hypervascularization [23, 24], and an abnormal inflammatory response [25]. Thus, investigating or analyzing the correlation between adenomyosis and fertility issues is challenging.

3. STATE OF KNOWLEDGE

3.1. MECHANISMS OF INFERTILITY ASSOCIATED WITH ADENOMYOSIS

1. Damage to the normal structure and function of the myometrium
2. Disrupted uterine peristalsis and sperm transport
3. Increased levels of free radicals
4. Hyperestrogenism
5. Hypervascularization
6. Abnormal inflammatory response

3.1.1. DAMAGE TO THE NORMAL STRUCTURE AND FUNCTION OF THE MYOMETRIUM

Uterine muscle cells affected by adenomyosis exhibit an altered ultrastructure compared to those in a normal uterus. A study on the ultrastructural characteristics of the myometrium in the presence or absence of adenomyosis revealed significant cellular-level changes. In cases with adenomyosis, cells in the junctional zone (JZ) showed cellular and nuclear hypertrophy, irregular shapes of nuclei and mitochondria, altered myelin bodies, and other pathologies [18]. These changes are associated with disruptions in the calcium cycle of the affected muscle cells, leading to the loss of normal uterine contraction rhythm and ultimately impairing uterotubal transport.

3.1.2. DISRUPTED UTERINE PERISTALSIS AND SPERM TRANSPORT

The directed movement of sperm toward the peritoneal opening of the fallopian tube on the side of the dominant follicle, dependent on uterine peristalsis, is crucial during the early reproductive period. This process relies on the structure of the circular muscle fibers of the myometrium [26]. In women with adenomyosis, the architecture of the myometrium is distorted due to the intrusion of endometrial glands and stroma. This leads to the development of hyperplastic muscle tissue, causing excessive myometrial peristalsis and increased intrauterine pressure [27]. Studies analyzing the relationship between uterine contraction frequency and fertility have shown a significant correlation. Higher uterine contraction frequency in both natural and stimulated cycles is associated with lower rates of conception, implantation, and live births [28, 29]. Additionally, myometrial hyperperistalsis and increased intrauterine pressure in women with adenomyosis, combined with elevated local hyperestrogenism, contribute to impaired implantation and abnormal placental localization, resulting in pregnancy loss [30].

3.1.3. INCREASED LEVELS OF FREE RADICALS

The implantation of a fertilized egg requires a low-oxygen environment in the uterus, as excessive free radicals can damage it and disrupt embryo development and, consequently, pregnancy [31]. The proliferative, early, and mid-secretory phases of the menstrual cycle in healthy women are characterized by varying levels of nitric oxide, xanthine oxidase, and superoxide dismutase. Women diagnosed with adenomyosis, however, exhibit a lack of variability in these levels and their excessive expression [32, 20]. Studies conducted on animal models have shown that an excess of free radicals in reproductive tissue inhibits both embryo development and implantation, thereby reducing pregnancy rates [33, 34]. Therefore, infertility in women with adenomyosis may stem from pathological levels of intrauterine free radicals.

3.1.4. HYPERESTROGENISM

Adenomyosis, as an estrogen-dependent uterine disorder, is associated with local pathological effects of steroid hormones. Aromatase enzyme expression is upregulated in adenomyotic tissue [35]. Studies have demonstrated exclusive expression of cytochrome P450 aromatase (P450arom) protein and mRNA in adenomyotic tissue and eutopic endometrium of patients with diagnosed adenomyosis. The function of P450arom is to convert androgens into estrogens [36]. Analyses comparing estradiol levels in menstrual blood to those in peripheral blood revealed a significant difference. Estradiol levels were found to be highest in menstrual blood from women with adenomyosis, while peripheral blood levels remained within normal ranges. This indicates a link between estradiol concentrations in menstrual blood and its local production in women with adenomyosis [37]. Furthermore, it has been shown that increased synthesis of P450arom enhances local estrogen production in the endometrium. Clinical pregnancy rates in women with elevated levels of P450arom mRNA in the endometrium are statistically lower [38, 39].

3.1.5. HYPERVASCULARIZATION

The vascular distribution in the endometrium of patients diagnosed with adenomyosis differs from that of patients without adenomyosis. Nearly half of women with adenomyosis exhibit abnormal vascularization on hysteroscopic examination, characterized by irregular vessel distribution and enlarged, reticular, or thick blood vessels. Morphometric analysis of the endometrium comparing the secretory and proliferative phases shows a significantly greater number of capillaries and overall vascular bed area in fertile women during the secretory phase [40]. In contrast, women with adenomyosis demonstrate significantly increased values for these parameters in both phases. Estrogens, acting via growth factors, are the most likely contributors to these vascular changes [41]. Angiogenic factors overexpressed in the ectopic and eutopic endometrial tissue of patients with adenomyosis include VEGF, follistatin, activin A, annexin A2 (ANXA2), and the TGF-β family. These factors promote vessel formation, increase permeability, and enhance collagen production due to repeated tissue damage and repair, ultimately leading to fibrosis in adenomyosis [42, 43, 44, 45].

3.1.6. ABNORMAL INFLAMMATORY RESPONSE

An increased number of macrophages and other immune cells in the endometrium of women diagnosed with adenomyosis activates the autoimmune system, leading to a dysregulated immune response [20, 46]. Macrophages produce pro-inflammatory cytokines such as TNF-α and IL-1, as well as reactive oxygen species, which have a toxic effect on the embryo [47, 48]. The disrupted immune response in adenomyosis may contribute to poor reproductive performance and implantation failure. Even after successful implantation, the embryo may be attacked by activated macrophages or T cells, resulting in miscarriage [20, 49, 50, 51].

3.2. TREATMENT OF ADENOMYOSIS AND REPRODUCTIVE OUTCOMES

The choice of treatment method largely depends on the patient's age, other factors affecting fertility, and the symptoms present. The limited number of studies with small participant groups makes it challenging to establish clear recommendations regarding adenomyosis and its impact on fertility. The primary indication for treating adenomyosis is symptoms that negatively affect the patient’s quality of life [52]. International guidelines for the pharmacological and surgical treatment of adenomyosis have not yet been developed [53]. The first-line treatments include nonsteroidal anti-inflammatory drugs (NSAIDs) and hormonal therapy. There is no treatment pathway that allows patients to conceive during symptomatic treatment of adenomyosis. Temporary symptom relief and regression of adenomyosis can be achieved with oral contraceptive pills, high doses of progestogens, a levonorgestrel-releasing intrauterine device (LNG-IUD), danazol, aromatase inhibitors, selective progesterone receptor modulators, and gonadotropin-releasing hormone (GnRH) agonists [54]. Regardless of the treatment method chosen, therapy for adenomyosis appears to positively influence fertility outcomes. Post-treatment, consistent improvements in pregnancy and live birth rates have been observed in patients with adenomyosis. In a study by Grimbzis et al., the reported pregnancy rates were 60.5% after complete adenomyosis excision, 46.9% after partial excision, and 55.6% following non-excisional methods [55].

Another study analyzed the effects of danazol-releasing devices, GnRH therapy, conservative surgery, and uterine artery embolization, showing significant improvement in pregnancy rates after treatment. A 41% pregnancy rate was achieved with a danazol-releasing device, spontaneous pregnancies occurred with GnRH therapy, a 36.2% live birth rate was observed after conservative surgery, and an 83.3% live birth rate followed uterine artery embolization [56]. GnRH analogs, characterized by their ability to reduce gonadotropin secretion, induce a localized hypoestrogenic effect, and exhibit antiproliferative properties. Treatment with GnRH is beneficial before frozen embryo transfer. A cohort study demonstrated an increase in live birth rates with an ultra-long GnRH agonist protocol compared to a long protocol [57]. A systematic review on GnRH stimulation showed a 40.7% pregnancy rate at 24 weeks after surgery involving GnRH therapy. In comparisons between long and short stimulation protocols, the long protocol significantly outperformed in pregnancy rates, live births, and miscarriage outcomes [58]. The impact of the above treatments may differ depending on whether a fresh or frozen cycle is used [59]. Surgically treating infertility associated with adenomyosis remains a controversial issue regarding its influence on reproductive outcomes. The most critical factors to consider include pathology removal, disease severity, and methods of uterine wall reconstruction. The primary postoperative complications are abdominal and intrauterine adhesions, placental attachment abnormalities, and uterine rupture. Several surgical options are proposed for treating women with adenomyosis: open or laparoscopic adenomyomectomy (total or partial), U-shaped sutures, overlapping flaps, triple-flap techniques, or transverse H-shaped incisions. For instance, a study on the triple-flap technique reported a pregnancy rate of 31.4% with no cases of uterine rupture [60]. Pregnancy rates ranged from 25.0% to 61.5%, while miscarriage rates were between 11.1% and 25.0% in women undergoing conservative surgical treatment for infertility [61]. Grimbizis et al. demonstrated that complete excision of adenomyosis in younger women was associated with a 50% live birth rate, whereas pregnancy rates were significantly lower in women over 40 years old [55].

4. CONCLUSION

This article aims to discuss the relationship between adenomyosis and infertility, analyzing the impact of this condition on the reproductive potential of women of childbearing age. Adenomyosis is a common gynecological issue that, as research indicates, is associated with lower pregnancy rates, reduced live birth rates, increased risk of miscarriage, and adverse outcomes both during pregnancy and the neonatal period. Adenomyosis often coexists with other conditions such as endometriosis or uterine fibroids, complicating its diagnosis and the assessment of its impact on fertility. Pathogenetic mechanisms associated with adenomyosis, as described in the literature, highlight its negative influence on endometrial receptivity and reduced expression of adhesion molecules critical for embryo implantation, ultimately contributing to difficulties in achieving pregnancy. This adverse effect is particularly evident in patients undergoing assisted reproductive procedures. However, the use of a long protocol with gonadotropin-releasing hormone analogs (GnRH-a) improves embryo implantation rates, making this approach a promising treatment method.

Preliminary GnRH-a treatment may also support attempts at natural conception. Surgical treatment of adenomyosis can improve fertility outcomes, although it carries risks of complications such as uterine rupture and intrauterine adhesions. Choosing the optimal surgical technique remains a challenge, and the available options require further investigation. The effectiveness of surgery in improving reproductive outcomes is still a matter of controversy. Even in cases of achieving clinical pregnancy, adenomyosis increases the risk of pregnancy complications, underscoring the need for more intensive prenatal care for affected patients. Proper diagnosis and treatment of adenomyosis are crucial to improving the quality of life and reproductive health of women. There is an urgent need for further research, including randomized controlled trials (RCTs), to better define the relationship between adenomyosis and infertility, develop effective diagnostic methods, and standardize therapies. Only robust scientific evidence will enable the creation of effective treatment protocols for women wishing to conceive despite a diagnosis of adenomyosis.

5. DISCLOSURE

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