Adenomyosis and Infertility

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Guoyun Wang

Uterine adenomyosis is a benign gynecological disease that affects women's fertility and quality of life. Infertility, miscarriage, and obstetric complications are prominent problems, which are difficult and hot spots in its research and treatment. There is an increasing evidence that adenomyosis is associated with infertility and reproductive failure [1–4]. A recent cross-sectional study of infertile women found that the incidence of adenomyosis was 29.7% in women over 40 years of age and 22% under 40 years of age. Furthermore, among people with repeated miscarriages and previous assisted reproductive technology (ART) failures, this proportion increased to 38.2% [5].

7.1 Factors Influencing Fertility in Adenomyosis

Infertility is the main clinical symptom in patients with adenomyosis. The possible mechanisms of infertility caused by adenomyosis are as follows: (a) Abnormal anatomical structure: adenomyosis often has an abnormal uterine cavity morphology, which may obstruct the fallopian tube opening, interfere with sperm transport and embryo implantation, or increased uterine volume compressing the surrounding fallopian tubes and ovaries, affecting the peristalsis of the fallopian tube and the function of collecting eggs in the pelvis, and thus affects the fertilization [6]. (b) The thickness of the endometrial-myometrial interface (EMI), or called junctional zone (JZ), increases, causing dysfunctional uterine peristalsis. Furthermore, the ultrastructure changes of the myometrium make the muscle cells contract abnormally, causing loss of rhythm of uterine contraction, leading to impaired sperm transport and affecting fertilization and embryo implantation [7]. (c) Adenomyosis is an

G. Wang (✉)
Department of Obstetrics and Gynecology, Qilu Hospital of Shandong University, Jinan, Shandong, China
e-mail: wangguoy@sdu.edu.cn

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inflammatory disease. Studies have found that patients with adenomyosis often have endometrial lesions, mainly endometrial polyps and endometritis. Endometrial polyps can cause disorders of embryo implantation, and the local inflammatory cells and factors in endometritis increase, killing and phagocytizing sperm interfering with the histocompatibility of embryos and the endometrium [8, 9]. (d) Endometrial dysfunction in patients with adenomyosis, including abnormalities in sex hormone synthesis and conduction pathways, decreased expression of implantation markers, reduced expression of adhesion molecules, changes in embryonic developmental genes (such as HOXA 10), increased release of free radicals, and endometrial vascularization disorders, etc., leading to abnormal embryo implantation and early abortion [10]. (e) Serum prolactin (PRL) levels in patients with adenomyosis are significantly higher than those in the control group. High levels of PRL can inhibit the secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), thereby affecting the function of the corpus luteum. High levels of PRL in the follicular phase can inhibit the synthesis and secretion of sex hormones, leading to disorders of follicular development, maturation, and ovulation. At the same time, the positive rate of PRL receptors in adenomyosis lesions is significantly increased, leading to an imbalance of sex hormones, which may lead to infertility [11].

7.2 Pregnancy Outcomes in Adenomyosis

Adenomyosis not only causes infertility but also affects pregnancy outcomes. Studies have found an increased risk of premature rupture of membranes and preterm birth in patients with adenomyosis [12]. The incidence of cesarean section, small-for-gestational age, postpartum hemorrhage, and fetal malpresentation in patients with adenomyosis also increased [13]. A current case-control study found that the incidence of second-trimester miscarriage, preeclampsia, and placental abnormalities in patients with adenomyosis also increased significantly [14]. Different types of adenomyosis have different effects on pregnancy outcomes. The incidence of pregnancy-induced hypertension and uterine infections in diffuse adenomyosis patients is higher than localized, and the incidence of cervical insufficiency is also increased [15]. These have led to an increased incidence of abortion, premature labor, and obstetric complications in patients with adenomyosis. These factors may end with secondary infertility in patients with adenomyosis.

7.3 Adenomyosis with Endometriosis

The influence of ultrasound classification of adenomyosis on infertility is also different. A prospective study by Exacoustos et al. 2019 [16] showed that localized lesions had a higher incidence of infertility than diffuse lesions, and that the prevalence of abortions in localized lesions involving the JZ was higher than that of diffuse lesions. Adenomyosis is often associated with endometriosis, especially in

infertile patients, and the proportion can be as high as 79% [17]. Pelvic endometriosis can cause dense adhesions of the ovary and fallopian tubes, leading to distortion of the fallopian tubes. In severe cases, the tubal obstruction can occur. When the ovarian endometriotic cyst ruptures, it can cause widespread inflammation, leading to omental adhesions and wrapping affecting the peristalsis of the fallopian tubes. The adhesion and encapsulation of the ovary affect the oocyte discharge. If the endometriosis destroys the ovarian parenchyma, it will affect egg production. Uterine adhesion makes it difficult for sperms to enter the uterine cavity and can also cause infertility. Besides, endometriotic lesions, involving the fallopian tube, can cause tubal obstruction, thereby affecting its function [18]. Patients with endometriosis often have neuroendocrine dysfunction, which leads to poor follicular development, impaired LH peak formation, or insensitivity of follicles to LH, or mechanical factors, such as adhesions, leading to luteinized unruptured follicle syndrome (LUFS), and endometriosis with LUFS accounts for about 18–79%. Endometriosis is also often associated with luteal dysfunction, with an incidence of about 25–45%. Luteal dysfunction is one of the causes of infertility in patients with adenomyosis and endometriosis. The peritoneal fluid of patients with endometriosis contains a large number of activated immune cells and cytokines, which can swallow sperm, affect sperm activity, hinder fertilization, and have apparent toxic effects on embryos, affecting early embryo development and implantation, causing infertility and early abortion. The peritoneal fluid of patients with endometriosis contains high concentrations of prostaglandin (PG). PG can cause abnormal uterine contractions and tubal peristalsis, so that by the time the zygotes reach the uterine cavity, it is not synchronized with the development of the endometrium and affect the implantation of the fertilized eggs, causing early abortion [19].

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