17 The Pregnancy Outcomes After Uterine Preservation Surgery and HIFU Treatment for Adenomyosis

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The clinical manifestations of adenomyosis are complicated, and there are many clinical treatments, but there is no single method that can resolve all the problems of adenomyosis. It is especially so for the treatment of patients with adenomyosis with infertility. Chen [1] emphasized that the treatment of adenomyosis should pay attention to the surgical techniques and the combined application of other treatment methods. Therefore, it is believed that the same principle should be applied for patients with adenomyosis and infertility, focusing on combined therapy.

At present, there is no consensus on the treatment of adenomyosis that will improve and preserve the patient's fertility. Gonadotropin-releasing hormone agonist (GnRH-a) long-term therapy combined with assisted reproduction has become the most commonly used method in clinical practice. Due to the complex etiology of adenomyosis, there are no recommendations to the surgical indication for patients with adenomyosis and infertility. Lang [2] proposed that in selected patients, surgical treatment can improve fertility outcomes. Patients with uterine adenomyosis can be selected for surgery if they meet the following criteria: (1) Ineffective medical treatment or other medical conditions that patients are not suitable for medical treatment. (2) Before assisted reproductive technology (ART) treatment, the uterus is large with focal lesions (adenomyoma). (3) No significant decrease in uterine or adenomyosis volume after GnRH-a pretreatment before ART or repeated embryo implantation failure.

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17.1 Uterine Preservation Surgery

Uterine preservation surgeries are divided into adenomyosis resection (adenomyomectomy) for localized adenomyosis and volume reduction surgery for diffuse adenomyosis. Resection of adenomyoma can remove the localized diseased tissue from the normal myometrium, which causes less damage to the surrounding normal myometrium. However, for diffuse adenomyosis, the volume reduction surgery requires the removal of a large piece of adenomyosis tissue, including intertwined healthy myometrial tissue. Thus the damage to the myometrium would be great. Whether conservative uterine preservation surgery should be performed on patients with adenomyosis is still controversial. The adenomyosis lesion is characterized by the aggressive growth of the adenomyosis involving the inner myometrial layer. While the surgeon attempts to remove the lesion completely, it may also cause the removal of a whole myometrial layer and damage the underlying endometrium, resulting in a large defect of the uterine myometrium and a uterus with weakened uterine wall, thereby increasing the risks of uterine rupture during pregnancy and labor. A serious complication, such as placental implantation, may also occur. When the adenomyoma is relatively focal, the pregnancy rate and live birth rate of patients after adenomyoma resection are higher. When the lesion is diffuse, it is necessary to analyze the situation and carefully evaluate the possible advantages and disadvantages of the surgery. Also, surgery should not only deal with the adenomyosis itself but the associated pelvic endometriosis, deep infiltrating endometriosis (DIE), uterine fibroids, etc. The extent and type of surgery may affect the outcomes of fertility and pregnancy.

17.2 Pregnancy Outcomes After Surgical Treatment of Adenomyosis

In 2018, “Endometriosis Management Guidelines” from the French Association of Obstetricians and Gynecologists and the French National Health Administration pointed out that the operation of uterine adenomyoma with a diameter of less than 6 cm did not improve the outcomes of fertilization, pregnancy, and birth rate. However, there is no related report of operations for adenomyosis with a diameter of more than 6 cm [3]. Therefore, this guideline did not recommend surgical intervention for patients with larger adenomyoma. However, there are also different opinions. Some small clinical studies had shown that patients with pre-operative infertility could have natural pregnancies after surgery, indicating that excision of uterine adenomyosis can play a role in promoting pregnancy. Since the first report of adenomyosis resection in 1990, more than 2000 cases of such patients have been reported worldwide in 2018, of which 89.8% were reported by the Japanese [4]. The emphases of the surgical methods were on the techniques of resection and suture. They are focal lesion resection, wedge resection, H-type resection, three-lobe suture, U-shaped suture, etc. Osada et al. [5] reported that 26 patients with fertility requirements had 16 successful pregnancies after resection of adenomyosis lesions,

14 full-term deliveries, and no uterine rupture. Saremi et al. [6] performed wedge-shaped resection of 103 cases of adenomyosis with severe symptoms (46 of which were infertile); 21 cases tried natural pregnancy after surgery, and 7 of them were successful. However, the number of these reported cases is limited, and the selection criteria are different. Clinically, there is a huge difference in the severity of adenomyosis combined with infertility, then who can benefit from the surgery remain controversial? Therefore surgery needs to be assessed carefully. Kishi et al. [7] analyzed multiple factors relating to the outcomes after conservative surgery. They found that the pregnancy rate of patients aged ≥40 years was significantly lower than that of patients under 39 years old (3.7% vs. 41.3%). For young patients, surgery may bring benefits. When the patient complains of severe pain symptoms, ineffective or failed medical treatment, complicated endometriosis, DIE in the pelvis, subfertility or repeated pregnancy failure, etc., if surgical treatment is to be performed, the patient should be carefully assessed and counseled for appropriate fertility surgery, emphasizing the implementation of individualized treatment.

The postoperative use of ART may increase the pregnancy rate. Still, age is an important factor affecting the pregnancy rate in patients with adenomyosis, especially those over 40 years old. The clinical value of conservative surgery is limited.

17.3 Pregnancy Outcome After Surgery for Focal Adenomyoma Is Superior to Diffuse Adenomyosis

Research data from Tsui et al. [8] showed that the pregnancy rate after resection of focal adenomyoma was 48.2% to 77.5%, the successful delivery rate was 26.8% to 69.0%; but, the pregnancy rate after diffuse adenomyosis is about 30% to 40%; nearly 1/3 to 1/4 of patients had a successful delivery. In the study of Grimbizis et al. [9], the pregnancy rate after complete resection of adenomyosis was 60.5%; the pregnancy rate after partial resection of the lesion was about 46.9%. Tan et al. [10] conducted a systematic review of 1396 cases of infertile women with focal and diffuse adenomyosis in 18 studies. The results showed that after focal adenomyoma resection, the average pregnancy rate, live birth rate, and miscarriage rate were 49.1%, 38.6%, and 27.6%; after surgical resection for diffuse adenomyosis, the above rate was 38.5%, 31.3%, and 16.2%. Therefore, for suitable cases, fertility-sparing surgery is effective in increasing the pregnancy rate, and the benefit after surgery for focal adenomyoma is superior to that of diffuse adenomyosis.

17.4 Surgery or Combined Drug Treatment Can Improve the Pregnancy Rate of Patients

Wang et al. [11] reported that resection of adenomyosis combined with GnRH-a in patients with adenomyosis and infertility could significantly prolong the period of symptom remission compared with GnRH-a alone. The 3-year cumulative pregnancy rate was high [46.4% (13/28) vs. 10.8% (4/37), P = 0.002], and

the 3-year cumulative successful delivery rate is high [32.1% (9/28) vs. 8.1% (3/37), P = 0.022].

17.5 Limitations of Conservative Surgery to Preserve Fertility

Surgical treatment of adenomyosis can improve fertility in some patients, but it also has limitations. Some normal myometrial tissues are missing after part of the adenomyosis is removed, and the normal myometrial tissue of the uterus is reduced during pregnancy, which can easily lead to miscarriage and premature delivery. Moreover, it is difficult to grasp the balance between removing the lesions as much as possible and maintaining the morphological integrity of the uterus. Conservative uterine surgery may lead to the damage of the uterine structure and the reduction of the uterine volume after the operation. A long period of contraception after surgery may further delay the timing of pregnancy. Besides, the probability of pregnancy complications during pregnancy increases, affecting live births. Uterine rupture is a complication of pregnancy and delivery after uterine surgery. In recent years, there were reports of uterine rupture during pregnancy after surgical excision of adenomyosis. Liu et al. [12] reported 114 cases of adenomyosis excision, of which 68 cases had pregnancies after the surgery, and 3 cases (4.4%) of them had ruptured uterus in pregnancy. Uncertainty in the extent of resection for diffuse adenomyosis may result in excessive resection of adenomyosis and the normal myometrium, resulting in a weak muscle layer, which becomes a high-risk factor for uterine rupture during pregnancy.

17.6 HIFU Treatment of Adenomyosis

HIFU is an emerging local non-invasive treatment method developed by combining the use of ultrasound in medicine with modern engineering technology. Ultrasound has characteristics, such as directivity, penetrability, and tissue sound absorption. HIFU uses these ultrasound characteristics and the biological effects of HIFU on ablating lesions. It accurately focuses the ultrasound energy emitted by the ultrasound transmitter onto the lesion in the body to destroy the lesion without damaging the surrounding normal tissues. The principle of HIFU's destruction of the lesion tissue is related to a series of biological effects of ultrasound. The most important of these is the thermal effect. HIFU can instantaneously raise the temperature of the lesion tissue at the focused site to above 60 ° C, thereby causing irreversible coagulative necrosis of the tissue. In addition, when the ultrasonic energy concentrates on the microbubbles developed from the heated up tissue, the microbubbles can be disintegrated, thereby instantaneously generating biological effects, such as cavitation effects resulting in high temperature and high pressure, which also play an important role in HIFU treatment. Also, the mechanical effect and dispersion effect of ultrasound certainly play an important role, and Yang et al. [13] had confirmed

that HIFU could also improve and raise the specific and non-specific immunity of the treated areas, thereby killing the diseased cells through the immune response.

17.7 The Impact of HIFU on the Reproductive Functions

In an early study, Yang et al. [14] performed HIFU ablation to the uterus of seven patients at open hysterectomy for adenomyosis. After removing the uterus, specimens were taken for pathological examination. Coagulative necrosis was found in smooth muscle cells, glandular cells, and interstitial cells of the adenomyoma. It provided a theoretical basis for the clinical application of HIFU in the treatment of adenomyosis. In 2006, Rabinovici et al. [15] reported a case of successful treatment of adenomyosis with MRI-guided HIFU. However, there has been a concern that because of the lack of a lesion boundary in adenomyosis, then the heat conduction can be relatively diffused and easy to cause the damage to the uterine myometrium and endometrium adjacent to the lesion, thereby affecting the patient's fertility. Therefore, for women with fertility requirements, HIFU was once contraindicated for the treatment of adenomyosis. However, more and more studies suggested that women who had HIFU ablation could also conceive naturally [15, 16]. Therefore, in 2009, the Food and Drug Administration (FDA) changed the absolute contraindication to the relative contraindication for patients with fertility demand to receive HIFU treatment.

Furthermore, some studies also showed that HIFU treatment has no adverse effects on pregnancy and newborns [15, 16]. At present, the safety of HIFU in the treatment of adenomyosis has been recognized. HIFU treatment under real-time ultrasound monitoring can accurately ablate adenomyosis lesions, minimize damage to normal uterine tissues, and create conditions for a successful pregnancy after treatment.

17.8 Pregnancy Outcomes After HIFU Treatment in Patients with Adenomyosis

To some patients with adenomyosis who have fertility requirements, HIFU, as an emerging treatment method, has a strong advantage in maintaining the integrity of the uterus. Using ultrasound focusing on ablating adenomyosis lesions, it can restore the anatomy of the uterus and improve the immune microenvironment, and the pregnancy rate has increased after HIFU treatment. Zhou [17] reported 68 cases of adenomyosis treated with HIFU. Among them, 62 were diffuse, and 6 were focal adenomyosis. There were 59 pregnancies in 52 patients after HIFU ablation treatment for adenomyosis, and the median pregnancy time after treatment was 10 months (range: 1-31 months). Among them, 21 had delivered at full term, including 17 cesarean sections and 4 vaginal deliveries. Two pregnancies were ongoing at the time of reporting; there were 31 abortions, including 20 spontaneous abortions and 11 induced abortions. Wang et al. [18] 2017 analyzed the pregnancy outcomes of 20

patients with adenomyosis who were successfully conceived after receiving HIFU ablation. The pregnancy to treatment time was from 1 to 23 months, with an average of 8.75 (± 6.23) months. Of the 20 patients, 18 were naturally conceived and 2 through ART. All patients had no serious complications during pregnancy. Eleven patients had cesarean sections, including one case of premature delivery, one case placenta previa, and nine cases selected cesarean section. All patients who had delivered had no complications, such as threatened uterine rupture or uterine rupture during delivery. Among the 20 patients, 3 were patients with primary infertility, and they had delivered at full term successfully. Luo et al. [16] studied 38 cases of adenomyoma patients who had fertility requirements and treated with HIFU ablation. A total of 15 patients out of the 38 patients were successfully conceived naturally after treatment. The average conception rate was 39.5%, and the conception time was 6 to 24 months. Among them, seven patients had delivered with three cesarean sections and four vaginal deliveries. Despite previous HIFU ablation, no obvious uterine abnormality was found during the cesarean sections. There were no uterine ruptures during pregnancy and childbirth. For the seven deliveries, the placenta detached spontaneously, and the uterus was well-contracted. The color Doppler ultrasound examination of the uterus also showed well involution with no abnormalities after 42 days of delivery. Tang et al. [19] analyzed the pregnancy outcomes of 30 patients with adenomyosis treated with HIFU and found that within 1 year after treatment, 24 of these 30 patients had a successful pregnancy and the pregnancy success rate was 80% (24/30). Among the 24 patients with a successful pregnancy, 18 cases (75%) and 6 cases (25%) underwent normal vaginal delivery and cesarean section, respectively.

From the above studies, we conclude that HIFU treatment is a safe and effective treatment for patients with adenomyosis and fertility requirements. HIFU treatment can improve their pregnancy rate, pregnancy outcome, and the pregnancy of patients with previous adverse obstetrical history. HIFU treatment of adenomyosis does not affect the patient's mode of delivery; thus patients with HIFU treatment can choose vaginal delivery without increasing the risks of complications during delivery. From the various reports in the literature, the best treatment to pregnancy interval can be shortened to 6-12 months after HIFU treatment.

17.9 Comparison of Pregnancy Outcomes of HIFU and the Conservative Surgery for Adenomyosis

It is still controversial whether the conservative surgical treatment of adenomyosis with uterine preservation can benefit patients who have fertility requirements. For some suitable patients, surgery can increase pregnancy rates and improve pregnancy outcomes. However, it must be targeted at patients with individualized analysis of their situation, e.g., a focal lesion, failed medical drug treatment, failed IVF-ET, and young patients with associated pelvic endometriosis or disorders; surgical treatment may then be beneficial. The time of contraception after surgery is much longer, because it needs time to allow the uterine wound to heal. Nevertheless, there is still

a risk of recurrence of the adenomyosis during contraception. Even after successfully pregnant, patients still have the risks of premature delivery, miscarriage, and uterine rupture during pregnancy and childbirth. Therefore, the indications for surgery have to be well-balanced of the pros and cons. As a new treatment for adenomyosis, HIFU treatment has only a limited number of studies. However, from the analysis of clinical data currently available, HIFU treatment can significantly improve the fertility and pregnancy outcomes. The increase in pregnancy and childbirth rate is no less than that of surgical treatment. Because HIFU treatment is a non-invasive treatment without any wounds, it therefore would not damage the integrity of the uterus and possibly not associate with postoperative pelvic and abdominal adhesions. HIFU treatment guarantees an intact structure of the uterus, thus it allows a shorter treatment to pregnancy interval time after HIFU treatment. It is another advantage that makes HIFU a preferred option for patients who have fertility requirements.

References

1. Chen C. Several problems that should be paid attention to in the course of uterine adenomyosis diagnosis and treatment. Chin J Pract Gynaecol Obstet. 2017;33(2):134–6.
2. Lang J. Several problems with uterine adenomyosis. Chin J Pract Gynaecol Obstet. 2017;33(2):129–33.
3. Li Xia YH, Wenxuan H, Wei C, Yumin Z, 2018 French Association of Obstetricians and Gynaecologists/French National Health Service. Endometriosis management guide. Chin Pract Gynecol Obstet. 2018;34(11):1243–6.
4. Xu B. The management status and prospect of uterine adenoid disease combined infertility. China Family Planning Obstet Gynecol. 2019;4:3.
5. Osada H. Uterine adenomyosis and adenomyoma: the surgical approach. Fertil Steril. 2018;109(3):406–17.
6. Saremi A, et al. Treatment of adenomyomectomy in women with severe uterine adenomyosis using a novel technique. Reprod BioMed Online. 2014;28(6):753–60.
7. Kishi Y, Yabuta M, Taniguchi F. Who will benefit from uterus-sparing surgery in adenomyosis-associated subfertility? Fertil Steril. 2014;102(3):802–807. e1.
8. Tsui K-H, et al. Conservative surgical treatment of adenomyosis to improve fertility: controversial values, indications, complications, and pregnancy outcomes. Taiwanese J Obstet Gynecol. 2015;54(6):635–40.
9. Grimbizis GF, Mikos T, Tarlatzis B. Uterus-sparing operative treatment for adenomyosis. Fertil Steril. 2014;101(2):472–487. e8.
10. Tan J, et al. Reproductive outcomes after fertility-sparing surgery for focal and diffuse adenomyosis: a systematic review. J Minim Invasive Gynecol. 2018;25(4):608–21.
11. Wang PH, et al. Is the surgical approach beneficial to subfertile women with symptomatic extensive adenomyosis? J Obstet Gynaecol Res. 2009;35(3):495–502.
12. Liu Wei ZM, Yanyan Y. Study on pregnancy after uterine adenoidectomy in infertility patients. China Medical Guide. 2017;14(8):92–5.
13. Yang R, et al. Effects of high-intensity focused ultrasound in the treatment of experimental neuroblastoma. J Pediatr Surg. 1992;27(2):246–51.
14. Yang Zhu CY, Lina H, Zhixuan W. High intensity focused ultrasound first study of pathological changes in adenomyosis in human body. J Clin Ultrasound Med. 2003;5(2):65–7.
15. Rabinovici J, et al. Pregnancy and live birth after focused ultrasound surgery for symptomatic focal adenomyosis: a case report. Hum Reprod. 2006;21(5):1255–9.

16. Luo S, et al. Pregnancy outcome after high intensity focused ultrasound (HIFU) treatment for patients with adenomyosis. Chongqing Med. 2014;4:454–455, 458.
17. Chunyan Z High-intensity focused ultrasound ablation to treat uterine adenomyosis - its effects and pregnancy outcome. Zunyi Medical College; 2017. p. 1-z.
18. Wang Zhi ZM, Li C, Yongbin D, Yu X. Observation of pregnancy outcome after high intensity focused ultrasound treatment in patients with adenomyosis. Chongqing Med. 2017;46(18):2506–8.
19. Tang B. Evaluation of the effect of high-intensity focused ultrasound ablation on adenomyosis patients with fertility requirements. J Contemp Med. 2019;17(19):76–7.