Case Report

Segmentation of *In vitro* Fertilization with High-intensity Focused Ultrasound in Repeated Implantation Failure with Adenomyosis

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Abstract

Adenomyosis is a complex issue in reproductive-age women not only on worsening of quality of life due to severe dysmenorrhea or heavy menstrual bleeding but also on the impact of infertility. A 39-year-old female, gravida 0 para 0, with a history of bilateral ovarian endometrioma post laparoscopic surgery presented to our hospital due to suspected deep infiltrative endometriosis (DIE), adenomyosis, and repeated implantation failure. Initially, gonadotropin-releasing hormone analog treatment for DIE with progestin-primed ovarian stimulation protocol was arranged. Four D5 blastocysts were obtained and freezed. Two frozen embryo transfer were performed after ultrasound-guided high-intensity focused ultrasound (USgHIFU) treatment of adenomyosis. She later had a dichorionic diamniotic twin pregnancy, and two healthy newborns were delivered by Cesarean section at gestational age of 35 weeks due to antepartum hemorrhage with placenta previa and preeclampsia. In conclusion, USgHIFU can be a potential treatment option in segmented *in vitro* fertilization in future.

Keywords: Adenomyosis, *in vitro* fertilization, segmentation, ultrasound-guided high-intensity focused ultrasound

Introduction

Generally, infertility is defined as the inability to get pregnant or conceive, despite unprotected sex, over the period of 12 months or longer. The prevalence of primary infertility increases with age and accounts for about 25% of married women around 35–40 years old, according to a national survey in the United States in 2013.

Adenomyosis is a disease characterized by endometrial stromal or glandular tissue infiltration into the myometrium with disruption of the junctional zone in histology. The condition not only causes heavy menstrual bleeding or severe dysmenorrhea but also is one of the contributing factors of infertility in about 6% of all infertile women.[1] Adenomyosis may have a negative impact on fertility through dysregulation of endometrium receptivity by affecting uterine peristalsis and endometrium receptivity.[2] It may cause repeated implantation failure during *in vitro* fertilization (IVF). In addition, it causes heavy menstrual bleeding, severe dysmenorrhea, or chronic pelvic pain which leads to impairment of women's life quality. Therefore, gynecologists are still working on optimal managements of adenomyosis.

In recent years, ultrasound-guided high-intensity focus ultrasound (USgHIFU) or magnetic resonance-guided high-intensity focused ultrasound ablation played the role of an emerging noninvasive surgical intervention for treatment

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of uterine leiomyomas and adenomyosis. The ultrasound energy focused on the target tissue under real-time sonography provided thermal damage to destroy it. It had been proven to be safe and effective.[3,4] However, the role of USgHIFU in fertility is still under investigation.

Segmentation of IVF cycle, which refers to separated embryo transfer from the cycle of ovarian stimulation and oocyte retrieval, was designed to prevent ovarian hyperstimulation syndrome (OHSS). Nowadays, we use medical or surgical intervention for adenomyosis during the period of segmentation to achieve better disease control, thus creating a better condition for embryo transfer in IVF. Here, we present a case with adenomyosis with a history of repeated implantation failure, who successfully gave birth after segmented IVF with USgHIFU ablation followed by frozen embryo transfer.

Case Report

A 39-year-old female, gravida 0 para 0, with a history of bilateral ovarian endometrioma, received laparoscopic bilateral oophorocystectomy at the age of 33. During that time, her cancer antigen 125 (CA125) was 1067.0 mIU/ml and anti-Mullerian hormone was 2.94 ng/ml. She went through four courses of IVF treatment, which were all failed, before visiting our hospital.

At the age of 36, she visited our hospital due to suspected deep infiltrated endometriosis over the left adnexal region, which led to left-sided ureter obstruction and subsequent episodes of urinary tract infection. At the time, transvaginal sonography showed an asymmetrical thickened posterior uterine wall around 5.9 cm, compatible with posterior wall adenomyosis [Figure 1a]. Computed tomography further revealed a suspicious soft-tissue lesion at the left adnexal region with uterine and urinary bladder involvement, thought to be associated with left urinary obstruction and left pyelonephritis. Right ovarian teratoma was also found. Her CA125 then was 232.88 mIU/ml.

Due to her desire for pregnancy, she had conservative treatment of deep infiltrative endometriosis with gonadotropin-releasing hormone (GnRH) analog and planned to receive IVF treatment once the condition was suitable. She had ovarian stimulation with progestin-primed ovarian stimulation protocol. Dydrogesterone 10 mg (Duphaston®, Abbott, The Netherlands) three times a day was prescribed since day 1 of the cycle. Her D1 laboratory data revealed an E2 level of 55 ng/ml, FSH 12.6 mIU/ml, LH 5.8 mIU/ml, and P4 0.18 ng/ml. Corifollitropin alfa at a dose of 150 μg (Elonva®, MSD, The Netherlands) was injected on cycle D2. Clomiphene (YSP, Taiwan) 150 mg QD for 7 days was prescribed since day 2. On the 12th day, the largest follicle was 17 mm, followed by a single 14-mm follicle and numerous smaller ones.

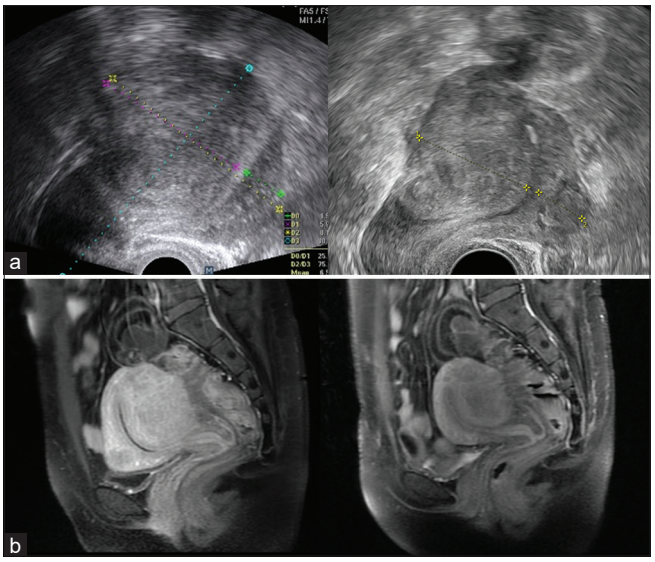

Figure 1: Endometriosis image finding of the patient. (a) Transvaginal sonography of the uterus before (right) and after (left) HIFU showed asymmetrical uterine wall and thickening of posterior uterine wall, indicating focal adenomyosis. The posterior wall thickness was 5.9 cm (right) and 4.1 cm (left). (b) T1-weighted MRI with contrast of uterus before (right) and after (left) HIFU showed thickening of the junctional zone and an ill-defined mass over the posterior uterus with multiple hemorrhagic foci in it, which was compatible with focal adenomyosis. The mass size was about 6.8 cm × 5.6 cm × 7.1 cm (right) and5.8 cm × 4.3 cm × 6.6 cm (left). HIFU: High-intensity focused ultrasound, MRI: Magnetic resonance imaging

Recombinant human choriogonadotropin alfa (Ovidrel®, Merck, Italy) was prescribed. Oocyte retrieval was performed uneventfully on the 14th day, during which four MII oocytes were obtained. Finally, four D5 blastocysts were obtained and frozen for future embryo transfer. Her CA125 level increased again, reaching 250 mIU/ml after ovarian stimulation, and she received GnRH agonist (Leuplin Depot 3M 11.25 mg®, Takeda, Japan), followed by Dienogest 2 mg/day (Visanne®, Bayer, Germany) treatment for adenomyosis.

At the age of 38, persistent adenomyosis with elevated CA125 level (266.7 mIU/ml) was still noted during follow-up despite medical treatment. Hence, USgHIFU ablation for adenomyosis was suggested. The PRO-2008 focused ultrasound-guided high-intensity focused ultrasound therapeutic system (SHENZHEN PRO HIFU MEDICAL CO., LTD, Shenzhen, China) with a 3.75-MHz diagnostic ultrasound probe (MyLab Class C, Esaote) was used for adenomyosis ablation as described in previous literature[5] [Figure 2]. The total sonication time was 1134 s. One dose of Leuplin Depot 3M 11.25 mg was prescribed after USgHIFU treatment immediately. The uterine volume shrinkage rate at 3 months after procedure was around 40% (preablation 210.1 cm^3, postablation 126.8 cm^3) [Figure 1b].

Four months after USgHIFU, two frozen D5 embryos (5AA and 2BB) were transferred. She had a dichorionic diamniotic

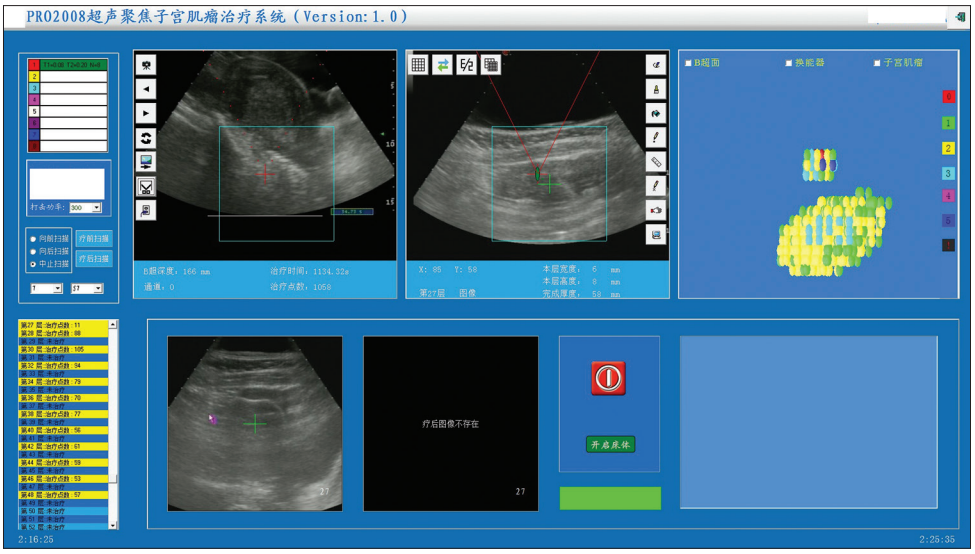

Figure 2: Schematic diagram of HIFU treatment of this patient. The interface of the operating system in USgHIFU treatment. USgHIFU: Ultrasound-guided high-intensity focused ultrasound. HIFU: High-intensity focused ultrasound

twin pregnancy and Cesarean section at gestational age of 35 weeks due to antepartum hemorrhage with placenta previa and preeclampsia. The twins were delivered with Apgar score (8 at 1 minute and 9 at 5 minutes for both twin) with birth body weight (2080 gm, 2175 gm). Both children were discharged from the hospital in a healthy state. After giving birth, she kept regular follow-up for right ovarian teratoma and took medication for adenomyosis without further surgical intervention.

Discussion

Adenomyosis is an important issue in women with infertility. The dysfunctional junctional zone is not only associated with a lower implantation rate and higher spontaneous abortion rate but also related to poor IVF outcomes.[6] Segmentation of IVF, which refers to freezing of the embryos after oocyte retrieval for transferring later, was originally designed to prevent OHSS during IVF cycle. Pretreatment of GnRH agonist showed beneficial effects in pregnancy rate.[6] Moreover, frozen embryo transfer resulted in a higher clinical pregnancy rate, implantation rate, and live birth rate than fresh embryo transfer in adenomyosis patients.[7] Thus, segmented IVF with freeze-all strategy and management of adenomyosis were applied to this patient to achieve better fertility outcomes.

Surgical treatment for cytoreduction of adenomyosis is a choice for women with desires of pregnancy. However, the risk of uterine rupture during pregnancy after adenomyomectomy, with the percentage of 3.6% in the literature, is higher than nonscarred uterus, vaginal birth after Cesarean section, and pregnancy after myomectomy.[8] There are also higher Cesarean section rate, preterm birth rate, and more pregnancy complications after adenomyomectomy. Moreover, short interval between pregnancy and uterine surgery may result in higher risk of uterine rupture during pregnancy. It is suggested that patients need to wait for a period of time before getting pregnant after surgery.[9] In conclusion, better management options are needed for these patients.

The primary goal of USgHIFU is direct volume reduction of adenomyotic tissue achieved by ultrasound energy. Symptoms such as dysmenorrhea can be relieved after USgHIFU ablation while the reproductive outcomes were still unclear. Nevertheless, the evidence of USgHIFU in adenomyosis is still limited. Huang *et al*. reported a comparison study with reproductive outcomes of 93 adenomyosis patients receiving USgHIFU or laparoscopic adenomyomectomy. The results indicated better spontaneous pregnancy rates with a higher rate of cesarean section in patients receiving USgHIFU. Uterine rupture was not reported in the study.[10]

Endometrial receptivity is determined by synchronized communication between decidualization endometrium and developing embryo. Genetic factors, immune responses, and complex autocrine and paracrine signals are all involved in the process of implantation. Uterine peristalsis, which is related to sperm and embryo transportation, also contributes to conception and embryo implantation. All the mechanisms above are potentially influenced by adenomyosis, which in turn may lead to implantation failure and infertility.[2]

In conclusion, segmentation of IVF is an important method for infertility patients. Among them, USgHIFU treatment in adenomyosis is potentially a useful alternative to surgeries for these patients due to less adenomyomectomy adverse outcome, such as uterine rupture, and a shorter time interval

needed before embryo transfer after surgery. Future research is still necessary.

Declaration of patient consent

The authors certify that they have obtained appropriate patient consent form orally. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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