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Prognosis of direct pregnancy in untreated atypical endometrial hyperplasia: a case report

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Abstract. – BACKGROUND: An increasing number of atypical endometrial hyperplasia (AEH) or endometrial cancer (EC) patients with fertility requirements choose conservative management, such as oral high-dose progesterone. Most of them use assisted reproductive technology (ART) to become pregnant after experiencing remission. However, the outcome of pregnancy is not ideal, probably because of long-term drug application in large doses or invasive uterine cavity treatment.

CASE REPORT: We presented a case of AEH who underwent direct pregnancy with good results without any treatment for her pathological endometrium. We described her endometrial histological results pre-and post-pregnancy in detail, hitherto absent from reports on this topic.

CONCLUSIONS: Patients with a strong desire to bear children at the time of an AEH diagnosis could consider taking 1-2 years to try a pregnancy before treating their AEH.

Key Words:
Atypical endometrial hyperplasia, Pregnancy, Preserved fertility, Assisted reproductive technology, Complete response.

Introduction

Fertility preservation treatment is becoming increasingly important in China due to the country's three-child policy. On the other hand, most women in childbearing age with endometrial hyperplasia (AEH) or endometrial cancer (EC) have not completed childbirth at the time of diagnosis, and therefore an increasing number of patients with AEH/EC have a strong desire to preserve their fertility[1,2]. However, frequent uterine cavity surgery is likely to cause mechanical damage to the endometrium during treatment, resulting in a lower live birth rate[3-5]. Given that AEH is only a precancerous lesion and that once a pregnancy is successfully conceived there is prolonged exposure to high levels of progesterone, pregnancy through assisted conception techniques may be considered for those infertile women diagnosed with AEH prior to receiving medication[6].

Here, we report a rare case of an elderly infertile woman diagnosed with AEH who became pregnant before taking any treatment, showing a satisfactory outcome in terms of both disease and fertility.

Case Presentation

In March 2016, a 37-year-old woman came to our fertility center for assisted reproductive technology due to infertility. For the past two years, she had experienced irregular menstrual cycles. Her body mass index was 27.68 kg/m^2. She denied any history of dysmenorrhea or any neoplastic disease in the family.

Ovulatory dysfunction and a space-occupying lesion in the uterine cavity were found during ovulation monitoring with ultrasound. Then, she turned to another hospital for hysteroscopic surgery, and the pathological report showed endometrial polyps. She obtained four embryos in total through two cycles of ovulation induction. In March 2017, when she planned the embryo transfer, the ultrasound again showed a space-occupying lesion in the uterine cavity, and she underwent a second hysteroscopic surgery. The patient's pathology report from the second hysteroscopic biopsy was misplaced, and she believed it was just another endometrial polyp, so she underwent embryo transfer after a freeze/thaw cycle as planned. Four weeks after transplantation, obstetric ultrasound revealed a single pregnancy sac and a fetal heartbeat. This time, she suddenly discovered that the pathology report from the second surgery showed atypical

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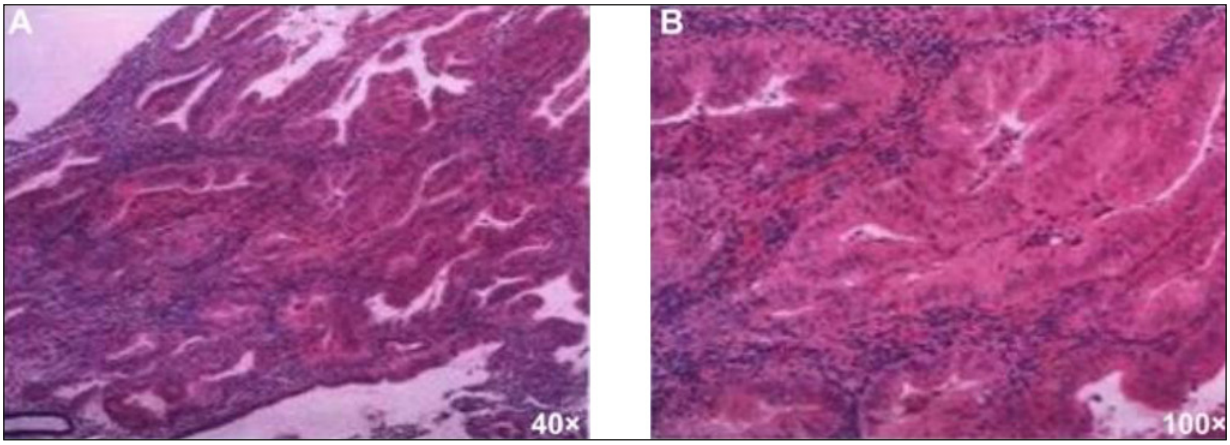

Figure 1. Atypia endometrial hyperplasia detected in the second biopsy on March 14, 2017 (stain: hematoxylin and eosin). **A**, Image showed at 40× magnification. **B**, Image showed at 100× magnification.

endometrial hyperplasia with the following immunohistochemical findings [ER (60% ++++), PR (90% ++++), p53 (wild type), PTEN (no mutation), Ki-67 (15% +)] (Figure 1). After being informed of the possible risks of disease progression, the patient chose to continue the pregnancy and signed an informed consent form.

During the pregnancy, she had gestational diabetes mellitus and controlled her blood glucose through diet and moderate exercise. In March 2018, at 40 weeks of gestation, she was hospitalized for spontaneous labor after rupture of the membranes and successfully vaginally delivered a full-term mature live male infant, with weight of 3,340 g, length of 49 cm, and Apgar score of 10. Six months after delivery, menstruation resumed, and abnormal uterine bleeding occurred. She underwent the third diagnostic hysteroscopy, and the pathological report still showed atypical hyperplasia [ER (80%), PR (80%), PTEN (focal lesion area), and Ki-67 (10%)] (Figure 2). Surprisingly, the extent was more limited than before. After taking medroxyprogesterone orally for six months, the pathology report showed a complete response, and there has been no recurrence thus far after regular review. Interestingly, after the complete response of her endometrial lesions, she was transplanted with the remaining embryos of good quality in August 2020 and failed to become pregnant.

Discussion

AEH refers to excessive endometrial gland hyperplasia accompanied by cellular atypia, which

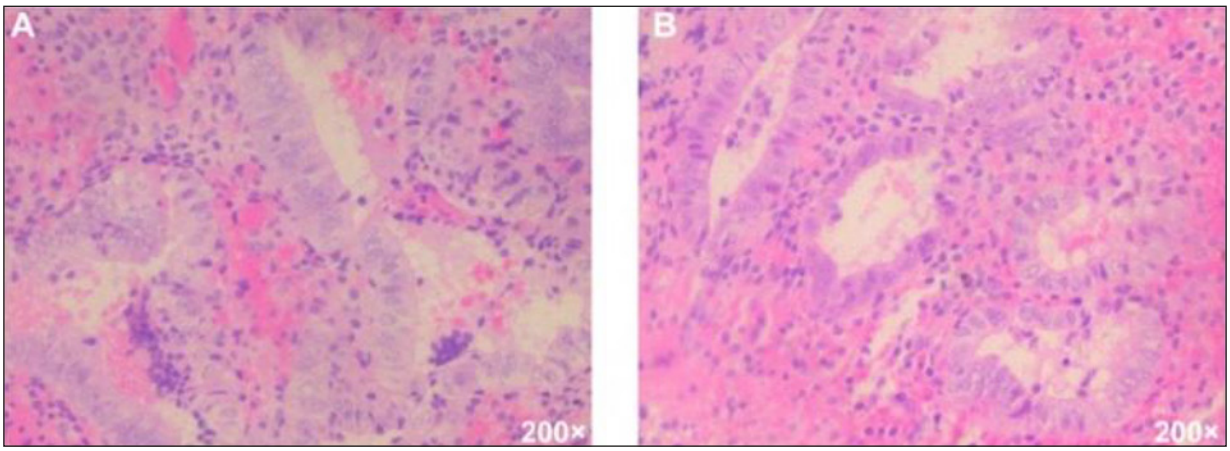

Figure 2. Most of endometrium showed proliferative changes and focal atypia six months after delivery on December 25, 2018 (stain: hematoxylin and eosin). **A**, Image showed at 200× magnification. **B**, Image showed at 200× magnification, but they are the different location of the endometrial tissue.

is a noninvasive endometrial precancerous lesion. Risk factors associated with the progression of endometrial hyperplasia include age >35 years, obesity, ovulatory dysfunction, metabolic syndrome, PCOS, tamoxifen treatment, and so on[7,8]. The symptoms are irregular menstruation and abnormal vaginal bleeding[9]. This patient presented some of the risk factors, including advanced age, overweight, ovulatory dysfunction, irregular menstruation, and infertility[10,11]. This case report describes a woman diagnosed with AEH who was not receiving any treatment. However, not only did she successfully conceive and deliver through assistive technology in just one year, but the endometrial lesions did not progress but became more localized.

Although the long-term risk of endometrial cancer in AEH is significantly increased, with 28% of AEH cases progressing to EC within 20 years, which suggests a need for treatment, a previous study reported[12] that women with AEH had only an 8.2% risk of progressing to EC within 1 to 4 years, and the average time to progress to cancer was 3 years. Several earlier studies[13,14] have described the disease progression of AEH without intervention. For instance, Robert et al[13] followed up 48 AEH patients for 5 or more years, among which 58% had regression, 19% had persistence, and 11 cases (23%) progressed to cancer. The progression time of these 11 patients with AEH was 4.1 years. Tabata et al[14] followed up 12 patients diagnosed with AEH and treated with curettage once a year; only 1 case was upgraded to early endometrial carcinoma in the third year of follow-up, and the prognosis was good after surgical resection. The patient in this case experienced ovulation induction, pregnancy, and lactation over a year after diagnosis, and her endometrial lesion had not progressed. Pregnancy, considered a natural, high-dose progestin therapy, may be a positive factor in treating lesions and preventing recurrence and may be supposed to act *via* shedding of the pathological endometrium, which occurred with every delivery and could be equivalent to curettage[3,15,16]. Therefore, for those patients with a strong desire for fertility once diagnosed with AEH, they could consider taking 1-2 years to try a pregnancy before treating their AEH.

Some studies[4,5] have suggested that the rates of clinical pregnancy and live birth among AEH patients after fertility preservation therapy are significantly lower than among patients without endometrial diseases. The possible reasons are that, on the one hand, female fecundity declines with age, and this factor should guide decision-making. Immediate IVF may be considered a first-line treatment strategy in women older than 38 to 40 years[17] since fertility preservation treatments for AEH take a considerable amount of time; in addition, repeated invasive intrauterine procedures during treatment can lead to endometrial thinning and affect the receptivity of the endometrium[3,5]. In this case, the patient was diagnosed with AEH at the age of 37, and without undergoing any treatment for her AEH, she underwent *in vitro* fertilization-embryo transfer, which resulted in a successful pregnancy. She then started treatment for her AEH, and by the time the lesion had completely degenerated, she was 40 years old, and she failed to become pregnant after a second embryo transfer.

Certainly, since approximately 25 to 40% of people diagnosed with AEH also have endometrial cancer, this approach could raise some concerns. However, this diagnosis is mainly based on the curettage method, and its accuracy needs to be improved[18]. With the development of a variety of diagnostic technologies, such as endometrial cytology[19], its accuracy has come into question when compared with comprehensive gynecological, ultrasound, MRI, and other examinations, so this concern may be unwarranted.

Conclusions

Since drug treatment requires a certain amount of time, fertility declines with age, and the endometrium is damaged by AEH treatment, there are poor pregnancy outcomes after treating AEH. The risk of AEH progressing to EC is very low, over 3 to 4 years. Thus, patients with a strong desire to bear children at the time of an AEH diagnosis could consider childbearing for one or two years before undergoing the treatment for their AEH.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Informed Consent

The patient was informed about the purpose and content of this study and signed the informed consent the consent to use the clinical data for this research.

Authors' Contribution

Conceptualization: JLW. Literature Search: LYZ, FFL. Clinical Data Collected: LYZ, FFL. Validation: LYZ, FFL, LT and JLW. Writing - original draft: LYZ. Writing - review and editing: LT, JLW. Supervision: JLW. All authors read and approved the final manuscript.

Ethics Approval

The study was approved by our Institutional Review Board (Approval number: 2020PHB063-01).

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