CASE REPORT

A Successful Fertility Outcome after Assisted Reproduction in a Woman with Endometrial Hyperplasia without Atypia Following Progesterone Therapy

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Abstract

Aim: The aim of the case report is to demonstrate a case of successful assisted reproductive technology treatment in a woman with endometrial hyperplasia without atypia.

Background: Endometrial hyperplasia (EH) is a premalignant lesion of endometrial carcinoma, and its incidence is three times higher than endometrial carcinoma. The impact of endometrial hyperplasia on fertility and advanced fertility treatments is not clear. However, the regression of endometrial hyperplasia without atypia following progesterone therapy has shown favorable fertility outcomes and is recommended before advanced fertility treatment.

Case description: A 41-year-old woman with a history of subfertility for 11 years and a history of heavy menstrual bleeding for 3 years, presented for assisted reproductive technologies (ART) treatment. Owing to heavy menstrual bleeding and persistently high endometrial thickness, she underwent a hysteroscopic assessment and endometrial sampling, which revealed endometrial hyperplasia without atypia. She was treated with six cycles of continuous oral progesterone and a repeat endometrial sampling after six months which revealed secretory endometrium. She underwent transfer of two embryos and had a singleton gestation. She had a successful pregnancy with an uneventful antenatal period and delivered a 2800 gm baby by elective cesarean section.

Conclusion: Disease regression should be achieved before starting fertility treatment and ART treatment is more successful compared with natural conception in a patient with endometrial hyperplasia.

Clinical significance: Even though there is no robust evidence to suggest endometrial hyperplasia without atypia has a negative impact on ART, free radical generation, and oxidative stress reactions shown in the pathogenesis of endometrial hyperplasia might negatively impact ART. Successful fertility treatment is possible after successful treatment of endometrial hyperplasia.

Keywords: Assisted reproduction, Endometrial hyperplasia without atypia, Progesterone therapy.

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Introduction

Endometrial hyperplasia (EH) is defined as the irregular proliferation of the endometrial glands with an increase in the gland-to-stroma ratio compared with proliferative endometrium. The incidence of EH is varied but estimated to be at least three times higher than endometrial carcinoma. The usual clinical presentation of EH is abnormal uterine bleeding such as heavy menstrual bleeding, intermenstrual bleeding, and unscheduled bleeding while on hormone replacement therapy and postmenopausal bleeding. Commonly, EH occurs in women between the ages of 50 and 60 years, nevertheless, the disease incidence in younger age groups is significant. The modern classification revised in 2014 has divided EH into EH without atypia and EH with atypia. The main diagnostic method is targeted biopsy and histological analysis of the endometrium. The impact of EH on fertility and fertility treatment outcome is not known but it may predispose women to infertility.

In this study, we report a case of a successful assisted reproduction in a woman whose EH without atypia was successfully treated with oral continuous progesterone for six months.

Case Description

A 41-year-old woman with a history of subfertility for 11 years, self-referred to assisted reproductive technologies (ART) treatment after unsuccessful basic subfertility treatment. Her past medical or surgical history was insignificant except for a history of heavy menstrual bleeding for 3 years, which had not responded satisfactorily to initial medical management. Her ultrasound scan revealed a low antral follicular count and an endometrial thickness of 16 mm on day 3 of menstruation. Her anti-Mullerian hormone was 0.5 ng/mL. Owing to heavy menstrual bleeding

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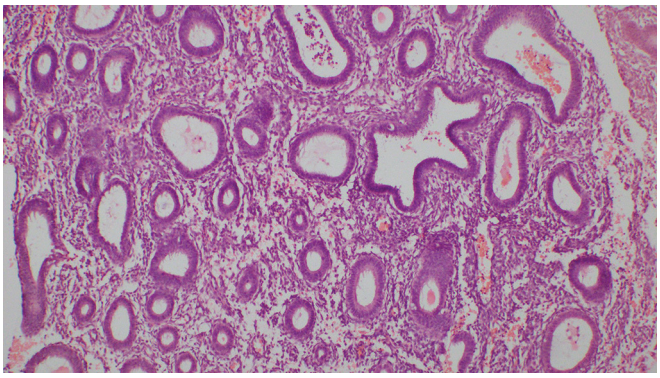

Fig. 1: Endometrial hyperplasia without atypia

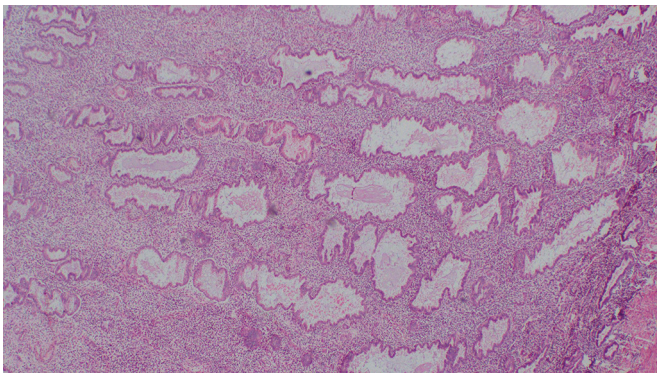

Fig. 2: Secretory epithelium

and persistently high endometrial thickness, she underwent a hysteroscopic assessment and endometrial sampling, which revealed EH without atypia (Fig. 1). She was treated with six cycles of continuous oral progesterone (Norethisterone 5 mg three times per day) and a repeat endometrial sampling after six months which revealed secretory endometrium (Fig. 2). She underwent transfer of two embryos and had a singleton gestation. She had a successful pregnancy with an uneventful antenatal period and delivered a 2800 gm baby by elective cesarean section. She had an uneventful postpartum period and was discharged with a follow-up plan of transvaginal ultrasound and hysteroscopy-assisted endometrial sampling six months postpartum.

Discussion

The pathological process of EH occurs when estrogen is unopposed by progesterone which provokes uncontrolled endometrial cell growth by binding to estrogen receptors in the nuclei of endometrial cells, which is supported by known risk factors such as increased body mass index, anovulation associated with the perimenopause or polycystic ovary syndrome, estrogen-secreting ovarian tumor, and drug-induced endometrial stimulation. Hyperplastic processes in the endometrium are considered precancerous conditions with different degrees of malignant potential.

Effective first-line treatments to achieving regression of EH without atypia are continuous oral and levonorgestrel-releasing intrauterine system [LNG-IUS] for six months duration.

As LNG-IUS causes a higher chance of disease regression, it should be considered as the first-line treatment compared with oral progestogens. Continuous oral progesterone is effective compared with cyclical oral progesterone in achieving disease regression. Endometrial surveillance should be made at least every 6-month interval with a target to achieve minimally two consecutive negative biopsies. As progestogen therapy induces histological and symptomatic remission in the majority of women with EH without atypia, hysterectomy is not considered as a first-line treatment. However, it is indicated in certain clinical conditions such as failure of histological regression of hyperplasia despite treatment, relapse of EH, and persistence of bleeding symptoms.

Currently, there is no robust evidence of a negative impact of EH without atypia on the ART treatment and its outcome. However, the involvement of oxidative stress reactions and free radical generation has been shown during the pathogenesis of EH in fertile women, and it may adversely affect the outcomes of ART in infertile women.

During the pathogenesis of EH, highly potent catalase, malondialdehyde, and xanthine oxidase have been demonstrated and support oxidative stress. Besides, unexplained depletion of total antioxidant capacity has been reported in unexplained infertile women and supports the link between antioxidants and infertility.[1] However, identifications of molecular and biochemical markers and prediction of ART treatment success have not been carried out by the above studies to strongly demonstrate the relevance between the pathogenesis of EH and fertility and ART treatment outcomes.

A few studies have shown positive outcomes of fertility treatment following disease regression after continuous progesterone therapy.[2] Therefore, women with EH who wish to conceive should ensure at least one disease regression treatment cycle before starting fertility treatment. This approach is supported by a NICE guideline which recommended early referral to a fertility specialist for optimal outcome, as a hyperplastic endometrium may predispose women to infertility.[3] Fertility outcome and relapse prevention are high in women with EH without atypia following ART treatment compared with natural conception.[4]

In our patient, she had primary subfertility with a history of heavy menstrual bleeding for 3 years and her endometrial thickness was persistently high even after medical management. The endometrial assessment was performed before embarking on ART treatment, and the histopathology report revealed EH without atypia. Histological regression of EH was achieved by 6 months of continuous oral progesterone therapy. Following this, she had a successful ART treatment and delivered a healthy fetus at term by the cesarean section.

Conclusion

In conclusion, the impact of EH without atypia on fertility and fertility treatments outcome, especially ART treatment is not clear. Current evidence suggests disease regression should be achieved before starting fertility treatment and ART treatment is more successful compared with natural conception. More attention needs to be paid to research EH and its impact on fertility and outcome.

Clinical Significance

Even though there is no robust evidence to suggest EH without atypia has a negative impact on ART, free radical generation and oxidative stress reactions shown in the pathogenesis of EH might negatively impact ART. Successful fertility treatment is possible after successful treatment of EH.

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