



Review Article

Reproductive advance of fertility preservation in patients with early endometrial carcinoma or endometrial atypical hyperplasia

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ABSTRACT

Endometrial cancer (EC) is the fourth common cancer in women worldwide with its incidence rising each year. 10%–15% young patients are diagnosed of EC. For patients of childbearing age with early endometrial cancer or atypical hyperplasia, it is necessary to consider surgical removal of uterus after they have given birth. It is a big challenge for reproductive doctors and oncologists to help such patients get pregnant safely as soon as possible. In this article, we will review the latest progress in conservative treatment and candidates for fertility preservation, application of molecular detection, the fertility outcome and follow-up treatment which aims to stimulate more thinking.

1. Introduction

Endometrial cancer (EC) is one of the most common gynecologic malignancies with its incidence rate increasing rapidly in recent years. Except for the increased incidence rate, the onset age of endometrial cancer is getting younger and younger. According to statistics, endometrial cancer patients with 14%–25% are premenopausal women, of which 5% of the patients are younger than 40 years old.¹ In 2019, Japan even reported a 14-year-old patient with endometrial cancer.²

Atypical endometrial hyperplasia (AEH) is a precancerous lesion of endometrial carcinoma including simple atypical hyperplasia and complex atypical hyperplasia. 29% of untreated complex atypical hyperplasia will develop into cancer, while 46% of patients with preoperative diagnosis of complex atypical hyperplasia will find adenocarcinoma in hysterectomy specimens.^{3–5}

The objective of this manuscript is to review the latest progress in the current management of patients with early EC or AEH who are candidates for fertility-sparing treatment. The molecular markers are discussed in the article which may promote the precise medicine in the future. Fertility outcomes of these patients are promising with assisted reproductive technologies which encourages the efforts of all participants

including doctors and patients.

2. Treatment regimen

The standard treatment for EC is fascial hysterectomy and bilateral salpingo-oophorectomy with or without lymphadenectomy.⁶ However, there are quite some proportion of young EC or AEH patients who have not yet completed childbearing with reproductive needs which causes contradiction. There is no denying that tumor is well-differentiated in young women in most cases which is frequently limited to the endometrium or superficial myometrium.⁷ It is suggested that child-bearing age patients who are qualified to preserve their fertility complete delivery as soon as possible before operation. Given the complicated situation, the exploration of fertility preserving protocols for early EC or AEH is a hot topic in recent years.

The exposing to high level of estrogens without the protection of progesterone is a risk factor for EC/AEH. Therefore, for young women who wish to give birth, progesterone therapy can reverse endometrial hyperplasia and EC by against estrogen-driven growth and proliferation which is recommended as the first-line treatment. The most commonly used one is oral medroxyprogesterone acetate (MPA) or megestrol

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acetate (MA), which is also the most classic treatment in each guideline. The commonly used dosage is 250–500 mg of MPA and 160–320 mg of MA daily. Previous studies also reported the doses of 800 mg of MPA and 480 mg of MA which vary in different hospitals. However, there are no differences found in studies comparing these different doses of MPA and MA.⁸ Patients receiving conservative therapy are supposed to check the endometrial biopsy each 3 months. The surgical treatment should be considered if the lesions are consistent in 9–12 months since the initial treatment. The progestin therapies vary from 3 to 36 months which is published in many studies, while most cases can have the reversal of endometrial lesions after 3–6 months of medication. Newest studies reviewed patients undergoing fertility-sparing treatment (FST) for early EC from 2005 to 2008 by comparing the cumulative complete response (CR) rates according to FST duration.⁹ This study found that 15 months of FST can be considered as the cutoff for optimal FST duration based on the maximal gain of CR increment if disease progression is excluded. Based on this study, the patients may hope to delay hysterectomy before complete reverse of endometrium. More randomized controlled studies are needed to assure the safety of FST with a long duration.

Despite of the benefits that progestins treatment bring, there are some accompanying side effects due to the progestins which includes increasing body weight, abdominal cramps, dizziness, venous thromboembolism and so on.¹⁰ When the patient is unable to tolerate the side effects of high-dose progesterone, or the progesterone therapy could not achieve satisfactory therapeutic effect, other treatments can be considered including aromatase inhibitors, oral contraceptives, selective estrogen receptor modulators (SERMs), gonadotropin-releasing hormone (GnRH) agonists and levonorgestrel intrauterine device (LING-IUD).

In recent years, many scholars have begun to pay attention to the application of LING-IUD in AEH and early EC which can achieve similar disease alleviation rate as oral progesterone with higher compliance by avoiding a series of nausea and vomiting caused by oral high-efficiency progesterone.¹¹ Patients can accept endometrial biopsy to follow-up the effectiveness of treatment with the presence of LING-IUD in the uterine cavity. National Comprehensive Cancer Network (NCCN) guideline listed LING-IUD as one of the first-line treatment protocols.¹² In 2020, a 34-year-old female with AEH was reported to be diagnosed as EC (IIIB stage in FIGO) 2 years after using LING-IUD. In this domestic case report, the main site of EC was at the broad ligament of the uterus in the pelvis which may be related to the location of LING-IUD in the uterine cavity.¹³ This unique case report was not to deny LING-IUD as an alternative treatment for AEH but to raise concern for the risk of endometrial cancer. Until now, most evidence on the effectiveness of LING-IUD for endometrial lesions are from retrospective studies, more randomized controlled studies are needed to confirm the safety of LING-IUD in the application of endometrial lesions. The best conservative treatment requires clinicians to consider individual differences.

GnRH-agonist can induce reversible medical castration to withdraw the production of estrogen which can be applied in combination with progestin therapies as fertility-sparing treatment for early EC or AEH.¹⁴ There are also studies demonstrating that GnRH agonist alone or in combination with LING-IUD is more effective in obese patients.¹⁵ A pilot study suggested endo-myometrial hysteroscopic resection and LING-IUD as the alternative treatment in women with stage IA, grade 1 endometrioid EC since the encouraging outcomes in terms of effectiveness and safety.¹⁶ Another pilot study presented a new option for fertility-sparing treatment in strictly selected patients with EC with superficial myometrial invasion. This study reported three women with well-differentiated grade 1 endometrioid adenocarcinoma of the endometrium with minimal myometrial infiltration who were treated with hysteroscopic resection and hormone therapy which has a positive outcome based on the 5-year follow-up and achieved pregnancies.¹⁷

In order to better summarize the fertility preserving protocols for EC/AEH, Guillon S et al.¹⁸ did a meta-analysis in 2009 which included 76 studies about conservative treatment of EC/AEH of which 43 studies were retrospective and 22 studies were prospective studies including

1604 patients from 1983 to 2017. All treatment schemes included MPA, MA, LING-IUD, GnRH-a, letrozole and others. This analysis used the remission rate as the primary outcome which was found to have no significant differences in each protocol. The best conservative treatment is still controversial. However, the meta-analysis showed that hysteroscopy was the preferred method of endometrial sampling compared with the segmental or simple endometrial biopsy because of higher consistency of the final diagnosis and more removing of tumor tissue in hysteroscopy. Some studies have suggested that the resection of lesions combined with LING-IUD can be a better conservative treatment.^{7,18}

Metformin as a biguanide drug is prescribed for the treatment of diabetes (type 2) for its suppression of hepatic glucose production.¹⁹ Diabetes mellitus was reported to have no effects on the outcome of conservative treatment in EC/AEH.²⁰ Surprisingly, metformin has been reported to inhibit the growth of endometrial cancer by inducing apoptosis in endometrial cancer cell lines.²¹ Other molecular and genetic studies indicate that metformin is promising in the treatment of early EC.²² However, studies about addition of metformin give contradictory outcomes. A retrospective cohort study recently indicated that the co-administration of metformin and progestin in the setting of fertility-sparing treatment for women with EC/AEH was not associated with improved outcomes which included complete response rate or recurrence-free survival rate compared with progestin monotherapy.²³ Apparently, prospective studies are required to investigate the effectiveness of metformin in fertility preservation of young patients with endometrial lesions.

3. Candidates for fertility preservation

Delaying hysterectomy brings risk of progression or recurrence for young women with EC/AEH which makes it necessary to restrict female patients in preserving fertility.

Many guidelines and expert consensus have been issued on the fertility preservation of endometrial carcinoma. The commonly accepted treatment conditions should be met at the same time for fertility preservation^{24–26}: (1) pathological diagnosis of highly differentiated endometrial adenocarcinoma; (2) imaging evaluation (recommended magnetic resonance imaging, MRI) indicates that the lesions were limited to the endometrium without invasion of myometrium and extrauterine metastasis; (3) the patient's full informed consent. However, different guidelines vary in some details which will be discussed in the following part.

Many pathologists will detect progesterone receptor (PR) in endometrial specimens to indicate the effectiveness of progesterone therapy.^{27,28} Due to the limited clinical data, there is no definitive conclusion whether the patients with PR negative expression of EC/AEH are safe to preserve fertility function. Follow-up of patients with PR negative expression are needed to evaluate its safety and effectiveness.

The previous guidelines limit the age of women who tend to preserve fertility to less than 40 years since the consideration of risks of recurrence and infertility. In 2019, Chinese Research Hospital Association (CRHA) proposed that it was possible for patients less than 45 years old to preserve reproductive function which provided opportunities for women aged 40–45 years old.²⁹ However, patients in this age group often face the difficulties of poor ovarian reserve and decreased fertility which makes it hard to get pregnant.³⁰ The advantages and disadvantages of their fertility preservation require further and deeper discussion.

For EC patients with myometrial invasion, the Expert committee of Obstetrics and Gynecology of CRHA agreed that the conservation of uterus can be fully evaluated to be possible.²⁹ However, the allowed depth of myometrium infiltration was not verified. Guidelines in 2017 suggested that the fertility preservation is possible if the lesion invaded the myometrium less than 1/2.²⁶ Considering the risk of lesions progression or recurrence, the fertility preservation of such patients needs comprehensive evaluation of tumor experts, imaging experts and pathology experts and the patients' full understanding to make decisions.

4. Application of molecular detection

Predictive markers of response to conservative treatment of early EC or AEH are still lacking, longer menstrual cycles and infrequent menstrual bleeding appear as independent predictive factors for conservative treatment failure.³¹ The application of molecular markers in EC can help to distinguish the low-risk and high-risk groups which can benefit the selection of treatment options for oncologists. As a result, more and more scholars have begun to put emphasis on the application of molecular markers in young EC/AEH females to evaluate the risk of lesions progression or recurrence. A published study in 2019 suggested that the molecular typing of endometrial carcinoma may be closely related to the prognosis of young patients with endometrial lesions. The literature included 257 patients with EC who were less than 50 years old at the time of diagnosis. They were divided into four types based on the molecular subtype, including maximal marginal relevance (MMR) deficient (MMRd), protein coding (POLE) ultra-mutated (POLEmut), non-specific molecular profile (NSMP) and p53 abnormal (p53abn). Through retrospective study, the molecular classification is closely related to the clinicopathological parameters and outcome of EC (mainly be shown as progression free survival). The female patients with p53 wild type have the lowest diagnosis age and the highest body mass index (BMI). Patients with POLEmut have the best clinical outcome while patients with MMRd and p53 abnormal type are higher risky and more likely to receive chemotherapy.³²

The current National Cancer Network guidelines for genetic cancer suggest that all women with EC should be tested for MMR mutations. A multi-center study indicated that the recurrence was more common in MMR-deficient than MMR-proficient cases.³³ If there is a lack of MMR, it is suggested to complete the gene screening of Lynch syndrome. Once diagnosed as Lynch syndrome, the patient needs to receive genetic consultation to fully evaluate the situation.³⁴ The guidelines do not recommend whether such patients can preserve fertility. In a recent article among gynecological oncologists, the majority of clinicians did not support the choice of conservative management and fertility preservation in endometrial cancer with Lynch syndrome.³⁵

Except for the four types of molecular subtypes, there are many other molecular biomarkers included to investigate in the field of EC/AEH. Progesterone receptor (PR) has been indicated to show the effectiveness of progestin treatment.³⁶ However, a meta-analysis suggested that ER and PR expressions are predictive of response in EC or AEH with a LING-IUD but not with oral progestins.³⁷ In this study, ER and PR were not significantly predictive of response in the subgroup of patients treated with oral progestins with an RR of 0.62 (95%CI 0.13–1.41, $p = 0.55$) and 2.10 (95%CI 0.71–6.24, $p = 0.18$). However, negative expression of ER and PR were significantly predictive of poor response in the subgroup of patients treated with LING-IUD with an RR of 7.35 (96% CI 2.98–18.16, $p < 0.0001$) and 3.41 (95%CI 1.19–9.77, $p = 0.02$). Recently, Msh homeobox 1 (MSX1) is reported to be a significantly different expressed gene between resistant and non-resistant EC.³⁸ A weak stromal progesterone receptor B (PRB) expression was reported to be a highly sensitive predictive marker of both no response and recurrence of EC and AEH conservatively treated.³⁹ Further investigations of additional molecular markers such as mutational status of beta-catenin (CTNNB1), L1 cell adhesion molecule (L1CAM), estrogen receptor, phosphatase and tension homolog deleted on chromosome ten (PTEN) methylation status and other markers are needed to promote the risk stratification models in the future.⁴⁰ However, PTEN had been reported to be not useful as predictive marker of response to the conservative treatment of EC or AEH.⁴¹ Predictive molecular biomarkers for the application of LING-IUD, GnRH-a, or aromatase inhibitors will improve females' outcomes and advance the application of precision medicine in EC.⁴²

5. Fertility outcome

For young patients with EC/AEH, their reproductive age is limited. There is more evidence that young females with EC/AEH are more closely related to anovulatory infertility and obesity which makes them in need for assisted reproductive technologies to actively get pregnant.⁴³ The successful pregnancy rate was reported to be obtained in early EC patients with GnRH-a regimen.⁴⁴ Aromatase inhibitors can be chosen to induce ovulation as an assisted protocol which can reduce the estrogen level thereby reducing the stimulation to the endometrium so as to ensure the safety of ovulation promotion scheme. There are already relevant reproductive centers abroad using letrozole to promote ovulation in EC/AEH patients which obtain satisfactory pregnancy outcomes while the number of cases is limited.⁴⁵ More clinical and basic research is needed to explore ovulation promotion plan for EC patients.

The fertility outcomes of young EC/AEH women are of great concern. In 2019, the American Society of Obstetrics and Gynecology Oncology validated 4007 women with age less than 45 years old who were diagnosed as EC (3137, 78.3%) or AEH (870, 21.7%) between 2000 and 2014 through a large number of data in the health insurance database. In this cohort which with the median follow-up time as 4.5 years, 79.6% of patients received radical surgical treatment. Another 20.4% of all included patients received progesterone treatment among which 48.5% received hysterectomy in the follow up. After excluding patients who received hysterectomy less than two months after the progesterone treatment, the median time from diagnosis to hysterectomy was 380 days. The median age of patients who experienced live labor during the study was 36 years old, the median time from diagnosis to the first pregnancy event was 413 days and the average time from diagnosis to live birth was 756 days.

In the cohort receiving progesterone treatment, 15.5% of patients received assisted reproductive technology, while 54% and 50% of women who were pregnant or had live births during the study were treated with assisted reproductive technology. Many data indicated that reproductive potential of reproductive age patients with EC/AEH was more limited which reminded reproductive doctors to carefully conduct individual assessment of the possibility of pregnancy in each patient.⁴⁶

In the same year, Korean scholars reviewed studies about patients in IA stage of endometrium cancer who had fertility preserved. A total of 141 women under 40 years old were included of which 71 patients had achieved complete remission after using MPA or LING-IUD and 49 patients of them attempted pregnancy with a total live birth rate of 66.6%. The study also divided pregnant women and non-pregnant women as two groups which found that the disease-free survival period of pregnant women group was 26 months, and that of non-pregnant women group was 12 months proving the benefits of pregnancy in reducing cancer recurrence.⁴⁷

6. Follow up and treatment

NCCN guidelines in 2018 suggested that patients with EC should undergo hysterectomy after completion of childbirth and be reviewed regularly before fertility finished. According to the guidelines for diagnosis and treatment of EC, follow-up should be conducted every 3 months in the first year of diagnosis and every 3–6 months in the second year since then every 6 months in the third-fifth year. The follow-up included gynecological examination, the blood examination of serum CA125 level, transvaginal ultrasonography, hysteroscopy or endometrial biopsy, abdominal and pelvic computed tomography (CT).

CA125 and human epididymal 4 (HE4) are widely used in the clinical diagnosis of epithelial ovarian cancer, but CA125 will also increase significantly in benign diseases such as endometriosis which limit the application especially for women of childbearing age. HE4 has been recognized as having a higher sensitivity in the diagnosis of early EC

since 2011.⁴⁸ For young patients with endometrial lesions who delay the radical surgery, the monitoring of tumor markers can be strengthened during the follow-up of cancer. Once the tumor marker is found to rise, further detection will be carried out.

7. Conclusion

Overall, the exploration of fertility preservation for young EC/AEH patients is imminent because of the increasing incidence rate and younger age of onset. Guidelines at home or abroad are constantly updated while many details stay controversial. At present, the most preferred drug treatment is still MPA or MA. The application of LING-IUD and other drugs still need more safety assessment. The application of hysteroscopy in conservative treatment of endometrial lesions deserves more attention. Patients who chose fertility preservation are supposed to accept active assisted pregnancy therapy and pregnancy can improve the prognosis of the disease to some extent. Once pregnancy completed, patients need to undergo hysterectomy and bilateral adnexectomy as soon as possible.

Our study comprehensively shows the focus of fertility preservation in early EC/AEH which attract the attention of oncologists and reproductive doctors. However, the quality of reviewed studies is limited because most of the existing studies are retrospective studies or small sample prospective studies. More big-scale prospective studies are expected to explore the safety and effectiveness of fertility preservation in EC/AEH.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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