Gynecology and Obstetrics Clinical Medicine 1 (2021) 49–53

Contents lists available at ScienceDirect

Gynecology and Obstetrics Clinical Medicine

journal homepage: www.keaipublishing.com/en/journals/gynecology-and-obstetrics-clinical-medicine

Chinese expert consensus on fertility-preserving treatment for young women with early stage well differentiated endometrial cancer

Rong Zhou, Qun Lu, Guoli Liu, Yiqin Wang, Jianliu Wang *

Peking University People's Hospital, Expert Committee of Obstetrics and Gynecology of the Chinese Research Hospital Association, China

ARTICLE INFO

Keywords:
Fertility-preserving treatment
Young women
Endometrial cancer
Progesterone

ABSTRACT

For young women with early stage well differentiated endometrial cancer who have fertility desire, it is import to give comprehensive assessment before initiation of conservative treatment. Progestin based therapy with regular assessment of treatment efficacy can achieve a promising outcome. After complete remission patients are suggested with assisted reproductive technology or maintenance therapy depending on their immediate pregnancy plan. Hysterectomy is recommended for patients who have finished reproduction while re-treatment for recurrent cases should be carefully informed.

1. Introduction

Endometrial cancer (EC) is a common malignant tumor of the female reproductive system with an increasing incidence in China [1]. Although it generally diagnosed in post-menopausal women, approximately 7.1% are diagnosed between the ages of 20 and 44 years [2]. With the postpone of pregnancy and release of "two-child" policy in China, more than 50% of patients are nulliparous at the time of cancer diagnosis and such patients may have a strong desire to preserve their fertility. Therefore, there is a need for discussion about fertility preservation treatment.

Clinicopathological characteristics of young EC patients include the following.

(1) Patients usually present with irregular menstruation or bleeding. Obesity, polycyclic ovarian syndrome (PCOS), infertility are common predisposing factors.
(2) Histological type is mostly endometrioid adenocarcinoma (EA), which is considered to develop from atypical endometrial hyperplasia. Tumors are mainly well-differentiated (grade 1, G1) with positive expression of estrogen receptors (ERs) and progesterone receptors (PRs). Patients with such tumor(s) usually have good prognosis.
(3) For patients with G1 lesion and endometrium only involvement, the risk of lymph node metastasis is 1.43% [3]. For patients with stage IA G1 tumor, negative lymph vascular space invasion or without evidence of intraoperative extrauterine disease, the reported risk of combined ovarian synchronous cancer or metastasis is below 1% [4,5].

Based on the above features, conservative approaches can be feasible for these young stage IA G1 EC patients who have fertility desire. To achieve both tumor remission and fertility preservation, comprehensive assessment and appropriate treatment regimens are very important. In this article, we will present a Chinese guideline for management of endometrial cancer in patients with fertility desire. All the recommendations are reached after expert group discussions among the members of the Expert Committee of Obstetrics and Gynecology of the Chinese Research Hospital Association.

2. Indications

Patients undergoing fertility-preserving treatment for early EC should completely meet the following criteria.

(1) Patients with age ≤40 years old with a strong desire for fertility

* Corresponding author.
E-mail address: wangjianliu1203@163.com (J. Wang).

Publishing services by Elsevier on behalf of KeAi

https://doi.org/10.1016/j.gocm.2020.10.002

Available online 8 December 2020

(exceptional cases see note 1). (2) Histopathological type EA G1. (3) Tumor is confined to the endometrium, which is stage 1A without myometrial invasion confirmed by imaging examinations (exceptional cases see note 3). (4) Positive expression of both ERs and PRs. (5) Normal serum CA_{125} level (exceptional cases see note 5). (6) No contraindication for progesterone therapy. (7) Pretreatment assessment of fertility function. (8) Patients should be given fully informed consent and be able to adhere to a planned follow-up.

Notes

1) Age: For patients aged between 40 and 45 years who have a strong desire to preserve fertility function, fertility-preserving treatment can be provided after a sufficient assessment conducted by a multidisciplinary medical team and the patient is fully consulted on the possibility of pregnancy.
2) Imaging examination: Pelvic magnetic resonance imaging (MRI) is preferred. High-resolution MRI should show no myometrial infiltration or extrauterine pelvic metastasis. If abdominal metastasis is suspected on ultrasound, abdominal pelvic computed tomography (CT) should be performed. Low-dose chest CT can be used to exclude lung metastasis or primary lung cancer.
3) Myometrial infiltration: If well-differentiated EA with superficial myometrial infiltration, the risk of lymph node metastasis should be assessed by imaging examinations. If without any other high-risk factors, fertility preservation can be cautiously considered.
4) PR expression: Although it has been reported that pathologically PR-negative patients, about 50% can obtain complete remission after fertility-preserving treatment, according to the European Society of Gynecological Oncology (ESGO) statement [6]. However, it has been shown that absence of PR expression is a risk factor for poor outcomes in conservatively managed EC patients [7–9] so the PR condition should be monitored after the cancer diagnosis is made. The majority of the currently used guidelines recommend positive PR expression as a prerequisite and a cautious attitude must be taken for patients with weak or negative PR expression in determining if a fertility sparing treatment should be given. Our expert committee does not recommend to choose conservative treatment strategy in EC patients with negative PR expression.
5) Serum CA125: CA125 elevation suggests the possibility of distant metastasis. However, CA125 can also be influenced by diseases such as inflammation, adenomyosis, and endometriosis. If tumor metastasis can be excluded, CA125 elevation should not be a contraindication for fertility-preserving treatment; however, close attention should be paid to dynamic changes in CA125.
6) Pretreatment assessment of fertility function: Reproductive experts should be consulted before treatment. Excellent ovarian reserve function includes, follicle-stimulating hormone (FSH) < 12 IU/L on days 2–3 of menstruation, *anti*-Mullerian hormone (AMH) > 1.1 ng/ml, and basal antral follicle count (AFC) > 7.
7) Genetic consultation: Patients with family history of Lynch Syndrome-related cancer, or with loss expression of mismatch repair (MMR) protein by using microsatellite instability and immunohistochemistry testing, should receive genetic counseling or genetic testing. It is debatable whether patients with Lynch Syndrome could be offered fertility-preserving treatment.
8) Informed consent: Patients should be informed of all the risks of fertility-preserving treatment, including the failure of the conservative treatment, the possibility of hysterectomy, side effects of treatment drugs, and requests for close monitoring and assessment during treatment.

3. Initial assessment

3.1. Medical history

A detailed history of menstruation, marriage, childbirth, past treatment processes and responses, complications, and family history of diseases such as PCOS, infertility, Lynch syndrome, diabetes mellitus, and hyperlipidemia should be obtained.

3.2. Physical examinations and laboratory analysis

Assessed general characters should include body height, body weight, body mass index (BMI), waistline, waist-hip ratio, gynecological examinations, complete blood count, liver/kidney function analysis, fasting blood glucose, serum insulin, basic coagulation analysis, and electrocardiogram. If necessary, a 75-g glucose tolerance test can be performed.

3.3. Pathological diagnosis

Hysteroscopic biopsy for endometrial specimens is recommended. A thorough histological review performed by experienced gynecological pathologists is requisite. Pathological report should include the pathological type, tumor grade, and ER and PR expression status. If conditions permitted, patients are recommended to undergo molecular typing of the tumor. Protein expression of p53 gene mutation and mismatch repair (MMR) genes in specimens can be detected using immunohistochemistry. And the presence of polymerase ε (POLE) gene mutations can be detected using gene sequencing. If MMR protein deletion is detected, then patients could be offered genetic testing to exclude Lynch syndrome.

3.4. Color Doppler ultrasound and pelvic MRI examinations

We recommend Doppler and MRI as the two principal pretreatment imaging examinations to exclude myometrial invasion or potential distant metastasis. If ultrasound, or particularly MR gives any signs of deep myometrial infiltration or metastasis the patient should not be included in the conservatively treated cohort.

3.5. Assessment of medical history

Relevant comorbidities, such as diabetes mellitus, hypertension, obesity, metabolism disorders, and abnormal glucose and lipid metabolism before treatment.

4. Assessment during treatment

Every 12 weeks of treatment is considered as one treatment course. At the beginning of treatment, close follow-up should be performed once every 4–6 weeks. Endometrial thickness and signs of potential myometrial invasion should be investigated using transvaginal color Doppler ultrasound. During the following treatment, within one week of each new treatment course, ultrasound or/and MRI should be performed to assess the uterine size, endometrial thickness, possible presence of any muscular infiltration as well as local and pelvic conditions. At the same time, a hysteroscopic biopsy of endometrial specimens is recommended performed for the pathological assessment.

4.1. Assessment of treatment efficacy

Criteria for efficacy evaluation - both pathology and imaging

(1) Complete response (CR): Imaging shows no evidence of tumors observed in the pelvic cavity, abdomen, or chest. While on pathology examinations, no atypical endometrial hyperplasia or EA lesion is observed on histopathology. They present often complete atrophy and degeneration of the glands, loose interstitial edema, or a decidual-like reaction.
(2) Partial response (PR): Imaging examinations may suggest the shrinking of EC lesions. Endometrial glands are less dense; however, papilla and sieve-like structures can still exist. Atypia of the glandular epithelium is decreased. Pathological features include

the disappearance of epithelial stratification, reduced density, and nuclear chromatin thinning. Glands can exhibit significant secretion responses or metaplastic presentations, including squamous metaplasia, eosinophilic metaplasia, and mucous metaplasia.

(3) No response (NR) or no change (NC): Imaging examinations suggest no change of the tumor lesion. Pathology of tumor tissues shows no difference compared to the pre-treatment specimens, or visible residual lesion is still present. Endometrial glandular shows no degeneration or atrophy and no responding changes to progesterone.

(4) Progression of disease (PD): Imaging examination shows evidence of myometrial infiltration, extrauterine lesions, distant metastasis, or lymph node metastasis. Histological differentiation shows upgraded and cell atypia aggravated. Definite myometrial infiltration and vascular and/or nerve invasion appeared in tumor tissues.

(5) Recurrence: Imaging examinations suggest reappearance of tumor lesion in endometrium and/or myometrium, or lesions of endometrial atypical hyperplasia or EC appeared again after pathologically CR.

4.2. Assessment of side effects

Side effects include increased body mass, irregular vaginal bleeding, breast swelling or pain, loss of appetite, nausea, vomiting, skin rash, and thromboembolic disease. We also recommend to obtain regularly the patients' body mass, waist circumference, and waist/hip ratio, as well as monitoring liver and kidney function.

5. Treatment regimen

5.1. Drug treatment

5.1.1. Oral progesterone

High-dose progesterone is preferred. Currently, the most commonly used progesterone are medroxyprogesterone (MPA) and megestrol acetate (MA).

5.1.2. Common dose of progesterone

MPA at 250–500 mg daily or MA at 160–320 mg daily for oral administration. The dose can also be divided into twice or three times daily. During treatment, the dose can be increased or decreased within the above range, depending on whether patients have vaginal bleeding symptoms and the changes in endometrial thickness monitored by imaging examinations.

5.1.3. Efficacy of progesterone

Usually the tumor shows a response to progesterone after 12 weeks of treatment. Most patients achieve CR after 3–6 months' treatment, and the general CR rate is 58%–89% [10]. BMI considered to be associated negatively with treatment effectiveness. BMI $>35\ kg/m^2$ is related to increased risk of treatment failure and recurrence. It is reported that prolonged treatment time of >9 months, can increase the total response rate of treatment [11]. In comparison, higher doses of progesterone have not been shown to produce better treatment efficacy.

5.1.4. Side effects of progesterone

The common side effects of high-dose progesterone treatment include vaginal bleeding, weight gain, and elevation of liver enzymes. A small number of patients have allergic reactions, such as skin rash. Patients who cannot tolerate progesterone treatment can choose other alternative treatment methods, see 1.5.

5.1.5. Other drugs

When the pathology showed NR or PR, after 3–6 months' initial treatment, assessment of the tumor risks should be re-conducted. No matter if patients have unsatisfactory treatment response or cannot tolerate oral progesterone, the following regimens can be considered or used in combination: (1) subcutaneous injection of a gonadotropin-releasing hormone agonist (GnRH-a) at 3.6 mg/3.75 mg once every 28 days, (2) LNG-IUS, (3) oral administration of aromatase inhibitor, such as letrozole, at 2.5 mg once daily. (4) For patients with insulin resistance or BMI$\geq 25\ kg/m^2$, metformin is considered to improve the metabolic profile. The combined use of metformin at 750–2000 mg per day, may potentially improve the long-term oncological outcomes [12].

5.2. Surgical treatment

Hysteroscopic resection of focal endometrial lesions is the preferred surgical option. Surgical procedures can be used followed by oral progesterone, LNG-IUS, or GnRH-a treatment. The purpose of surgical management is to minimize the tumor load as much as possible and shorten the treatment time required to achieve CR. It should be noted that the operation duration and the distention pressure of uterine should be adequately controlled to prevent iatrogenic tumor spreading. Also, intrauterine adhesion should be carefully precautioned [10].

5.3. General treatment

EC patients usually combine with metabolic syndrome. It is recommended that weight loss to keep the BMI $\leq 25\ kg/m^2$, and stabilizing the level of blood glucose help improve the treatment efficacy.

5.4. Termination of treatment

Indications of patients who meet one of the following conditions should terminate fertility-preserving treatment and undergo hysterectomy: (1) patients with definite evidence of PD, (2) patients with NR on pathology after continuous treatment for six months, (3) patients who have had multiple recurrences, and (4) patients who no longer require fertility preservation or cannot tolerate conservative treatment.

Hysterectomy is recommended for patients who have finished reproduction or those who have disease recurrence. The reason is that for now, the cause of EC is still not clear. Although patients may achieve complete remission after treatment, the potential cause of EC has not been removed, and the risk of tumor recurrence and metastasis still exists. However, some patients persist to preserve uterus after they have finished reproduction. For those who have high-risk factors for recurrence, like patients with obesity, PCOS and other persistent high-level estrogen status, or who have longer treatment time to CR [13], we recommend hysterectomy. Otherwise, uterus preservation might be attempted after fully informed of the complexity and risks of tumor with patients. Nevertheless, these patients should receive life-long follow-up under close medical monitoring.

6. Management after completion of treatment

When patients achieve CR after initial treatment, a final consolidated 3 months treatment course is recommended. After twice continuous pathologically CR, patients are advised to prepare pregnancy as soon as possible. Assisted reproductive technology (ART) is recommended, but natural pregnancy can also be expected. For patients who temporarily do not have a pregnancy plan, maintenance treatment is recommended.

6.1. Assisted reproduction

Active assisted reproduction is recommended after patients have achieved CR. *In vitro* fertilization and embryo transfer (IVF-ET) is a relatively high-efficiency measure. However, there is no definite conclusion regarding the effect of high estrogen and progesterone status on EC during the ovulation induction process. Patients also need to be fully informed of the potential risks, and appropriate regimens should be

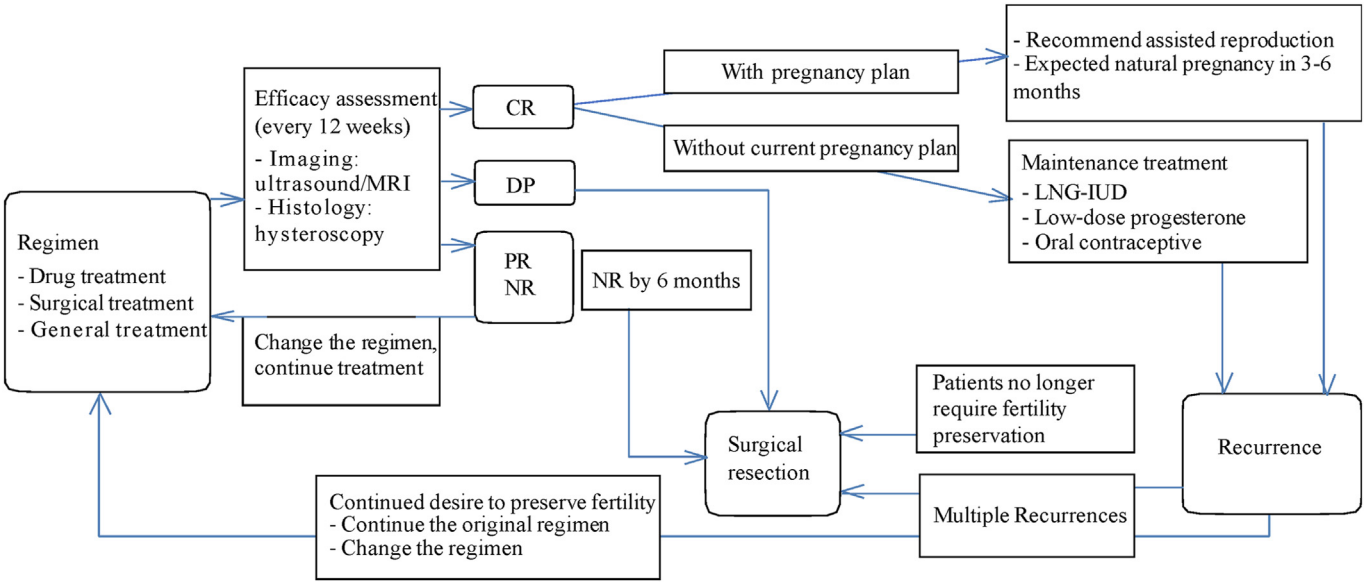

Fig. 1. Flow chart of fertility-preserving treatment for EC. CR: complete response; DP: disease progression; PR: partial response; NR: no response.

selected to control estrogen and progesterone levels during assisted reproduction treatment.

6.2. *Natural pregnancy*

Natural pregnancy allowed to be expected within 3–6 months. The expected period for natural pregnancy should not be too long. If patients fail to get pregnant after three months, relevant examinations and ART therapy should be timely performed. Because the spontaneous pregnancy rate of obese patients is significantly lower than that of non-obese patients, it is recommended that obese patients should actively lose weight, adjust their diet and lifestyle, and receive ART as soon as possible after CR.

6.3. *Maintenance treatment*

After CR, patients should receive maintenance treatment if temporarily not having a pregnancy plan to maintain regular menstruation and prevent disease recurrence. Maintenance treatment methods include levonorgestrel-releasing intrauterine systems (LNG-IUSs), low-dose cyclic oral progesterone (such as 20–40 mg/day of dydrogesterone for at least 10–12 days every month), and oral short-acting contraceptives, which can reduce the risk of disease recurrence. During maintenance treatment, ultrasound examinations should be performed every 3–6 months, and endometrial pathological examinations can be performed if necessary.

7. Re-treatment challenge after recurrence

The recurrence rate of EC after conservative management is 30%–40% [6] and the long-term remission rate is less than 50% [14]. The median time to recurrence is 15 months [6]. A significant number of patients will recur before having completed their family planning. Fertility-preserving re-treatment seems to be safe and efficient for these patients who got remission after previous treatment. We recommend a careful review of previous treatment response, disease assessment and fully informed of re-treatment risk with patients. Retreatment after relapse can still achieve the remission rate of 82%–90% [15], but may be lower than the initial treatment [16]. Patients may have certain chance of pregnancy after re-treatment [17]. In addition, it should be noted that patients with recurrence may have an increased risk of secondary recurrence [15,17]. Hysterectomy is recommended for patients with multiple recurrence who may have persistent systemic high-risk factors of EC and less possibility of future fertility.

The process of fertility-preserving treatment for EC is shown below (Fig. 1).

Additional contributing authors for the Chinese expert consensus on fertility-preserving treatment for young women with early stage well differentiated endometrial cancer:

Chunlin Chen (Nanfang Hospital, Southern Medical University), Xiaojun Chen (Obstetrics & Gynecology Hospital of Fudan University), Mian He (The First Affiliated Hospital, Sun Yat-sen University), Beihua Kong (Qilu Hospital of Shandong University), Rong Li (Peking University Third Hospital), Bin Ling (China-Japan Friendship Hospital), Congrong Liu (Peking University Third Hospital), Jihong Liu (Sun Yat-sen University Cancer Center), Ding Ma (Tongji Hospital, Huazhong University of Sciences & Technology), Jie Qiao (Peking University Third Hospital), Pengpeng Qu (Tianjin Central Hospital of Gynecology Obstetrics), Danhua Shen (Peking University People's Hospital), Huiru Tang (Peking University Shenzhen Hospital), Xiaoping Wan (Shanghai First Maternity and Infant Hospital, Tongji University), Gang Wang (The First People's Hospital of Foshan), Yi Wang (Peking University People's Hospital), Lihui Wei (Peking University People's Hospital), Yang Xiang (Chinese Academy of Medical Sciences and Peking Union Medical College), Xing Xie (Women's Hospital, Zhejiang University), Fengxia Xue (Tianjin Medical University General Hospital), Lijiang Xu (The First People's Hospital of Foshan), Huixiam Yang (Peking University First Hospital), Yuanqing Yao (The General Hospital of the People's Liberation Army), and Yu Zhang (Xiangya Hospital, Central South University).

Declaration of competing interest

None.

Acknowlegements

The study was supported by the National Key R&D Program of China (No.2019YFC1005200 and 2019YFC1005204) and National Key Technology R&D Program (No. 2015BAI13B06).

References

[1]. Wang Y, Yang JX. Fertility-preserving treatment in women with early endometrial cancer: the Chinese experience. *Canc. Manag. Res.* 2018;10:6803–6813.

[2]. Corzo C, Barrientos Santillan N, Westin SN, et al. Updates on conservative management of endometrial cancer. *J Minim Invasive Gynecol.* 2018;25(2):308–313.
[3]. Creasman WT, Odicino F, Pecorelli S, et al. Carcinoma of the corpus uteri: FIGO annual report on the result of treatment in gynaecological cancer. *J. Epidemiol. Biostat.* 2001;6:45–86.
[4]. Lee TS, Jung JY, Kim JW, et al. Feasibility of ovarian preservation in patients with early stage endometrial carcinoma. *Gynecol. Oncol.* 2007;104(1):52–57.
[5]. Ignatov T, Eggemann H, Burger E, et al. Ovarian metastasis in patients with endometrial cancer: risk factors and impact on survival. *J. Canc. Res. Clin. Oncol.* 2018;144(6):1103–1107.
[6]. Rodolakis A, Biliatis I, Morice P, et al. European society of gynecological Oncology task force for fertility preservation: clinical recommendations for fertility-sparing management in young endometrial cancer patients. *Int. J. Gynecol. Canc.* 2015; 25(7):1258–1265.
[7]. Yamazawa K, Hirai M, Fujito A, et al. Fertility-preserving treatment with progestin and pathologic criteria to predict responses, in young women with EC. *Hum. Reprod.* 2007;22:1953–1958.
[8]. Ehrlich CE, Young PC, Stehman FB, et al. Steroid receptors and clinical outcome in patients with adenocarcinoma of the endometrium[J]. *Am. J. Obstet. Gynecol.* 1988; 158(4):796–807.
[9]. Upson K, Allison KH, Reed SD, et al. Biomarkers of progestin therapy resistance and endometrial hyperplasia progression[J]. *Am. J. Obstet. Gynecol.* 2012;207(1): 31–36.
[10]. Wang Y, Yang JX. Fertility-preserving treatment in women with early endometrial cancer: the Chinese experience. *Canc. Manag. Res.* 2018;10:6803–6813.
[11]. Wang Y, Zhou R, Wang H, et al. Impact of treatment duration in fertility-preserving management of endometrial cancer or atypical endometrial hyperplasia. *Int. J. Gynecol. Canc.* 2019;29(4):699–704.
[12]. Mitsuhashi A, Habu Y, Kobayashi T, et al. Long-term outcomes of progestin plus metformin as a fertility-sparing treatment for atypical endometrial hyperplasia and endometrial cancer patients. *J Gynecol Oncol.* 2019;30(6):e90.
[13]. Chen M, Jin Y, Li Y, et al. Oncologic and reproductive outcomes after fertility-sparing management with oral progestin for women with complex endometrial hyperplasia and endometrial cancer. *Int. J. Gynaecol. Obstet.* 2016;132(1):34–38.
[14]. Gunderson CC, Fader AN, Carson KA, et al. Oncologic and reproductive outcomes with progestin therapy in women with endometrial hyperplasia and grade 1 adenocarcinoma: a systematic review. *Gynecol. Oncol.* 2012;125(2):477–482.
[15]. Park JY, Lee SH, Seong SJ, et al. Progestin re-treatment in patients with recurrent endometrial adenocarcinoma after successful fertility-sparing management using progestin. *Gynecol. Oncol.* 2013 Apr;129(1):7–11.
[16]. Wang Y, Yu M, Yang JX, et al. Prolonged conservative treatment in patients with recurrent endometrial cancer after primary fertility-sparing therapy: 15-year experience. *Int. J. Clin. Oncol.* 2019;24(6):712–720.
[17]. Yamagami W, Susumu N, Makabe T, et al. Is repeated high-dose medroxyprogesterone acetate (MPA) therapy permissible for patients with early stage endometrial cancer or atypical endometrial hyperplasia who desire preserving fertility? *J Gynecol Oncol.* 2018;29(2):e21.