

EDITORIAL

Gynecology

# A practical guideline on the fertility-sparing treatment of patients with endometrial carcinoma and atypical endometrial hyperplasia

The 2023 ESGO/ESHRE/ESGE guidelines represent a significant milestone in the fertility-sparing treatment of patients with endometrial carcinoma<sup>1</sup> However, a clear, practical guideline is still lacking in the published literature. Our goal is to provide a step-by-step approach for managing

patients diagnosed with endometrial cancer or atypical endometrial hyperplasia at reproductive age. We also offer detailed recommendations on the most appropriate endoscopic surgical techniques to use based on lesion type, as well as guidance on the preferred therapies (Figure 1).

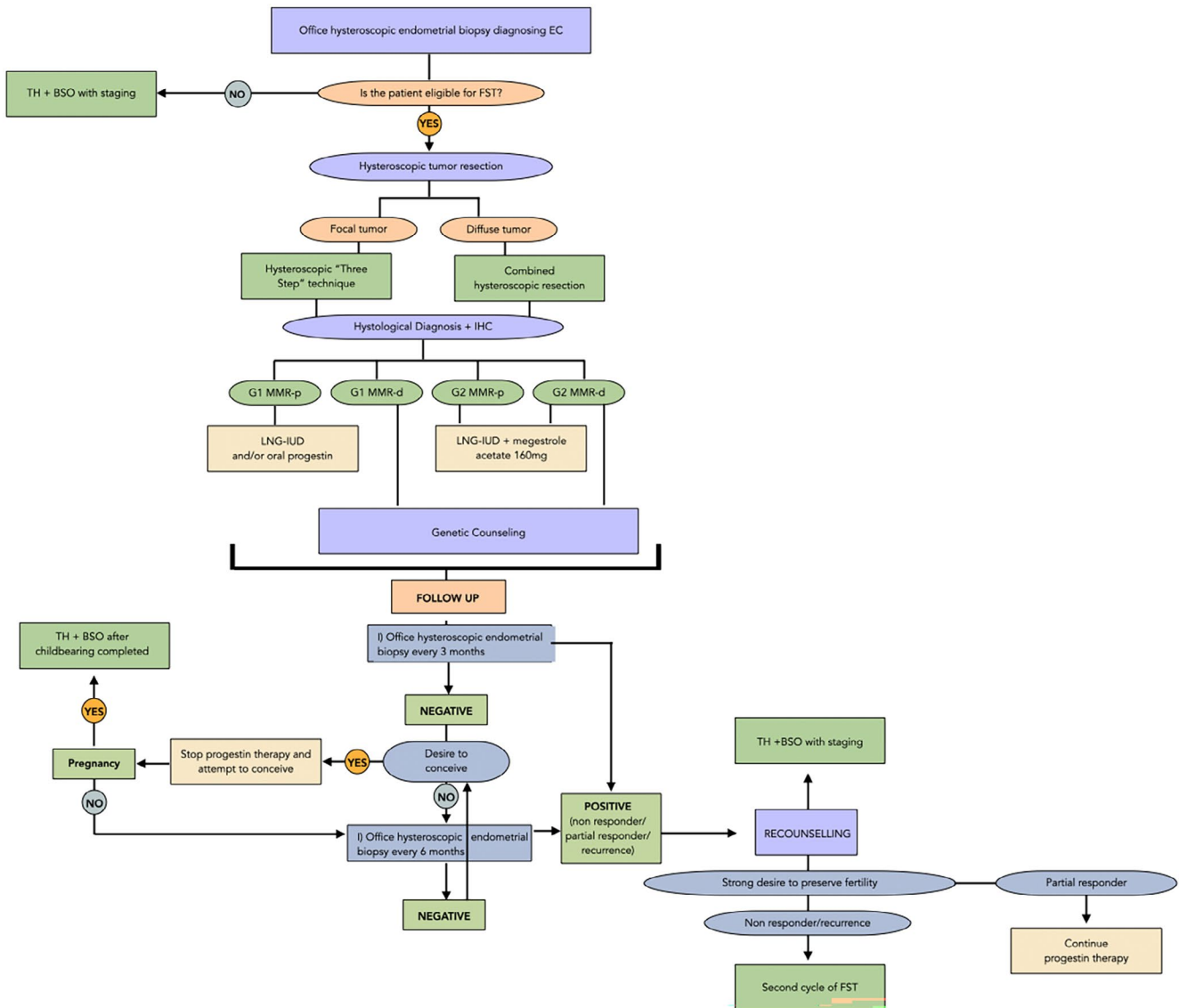


FIGURE 1 Suggested flow-chart for the fertility sparing management of women with endometrial cancer EC endometrial cancer; FST fertility sparing treatment; TH + BSO total hysterectomy + bilateral salpingo-oophorectomy; IHC immunohistochemistry; MMR-p mismatch-repair proficient tumors; MMR-d mismatch-repair deficient tumors; LNG-IUD levonorgestrel intrauterine device.

1. **DIAGNOSIS:** The gold standard for confirming the diagnosis of endometrial carcinoma is a hysteroscopic-guided endometrial biopsy. Patients eligible for fertility-sparing treatment (FST) are typically women under 42 years who wish to preserve their future fertility. Ideally, they should have grade 1 endometrioid adenocarcinoma with no evidence of myometrial invasion or adnexal involvement, as assessed by magnetic resonance imaging (MRI) or transvaginal ultrasound (TV-US) and no signs of pelvic or para-aortic lymph node involvement or distant metastases on MRI or computed tomography. The evidence for FST in women with grade 2 endometrioid adenocarcinoma is limited, so treatment decisions should be made on a case-by-case basis.
2. **COUNSELING:** Thorough counseling and informed consent are essential. The standard treatment for endometrial endometrioid carcinoma confined to the uterus is total hysterectomy, bilateral salpingo-oophorectomy, and surgical staging.<sup>2</sup> FST is not currently considered the standard of care. Patients should be properly informed about the follow-up process and understand that definitive surgery is recommended once childbearing is complete.
3. **RISK FACTORS:** Obesity is strongly associated with the development of endometrial cancer. Other risk factors include nulliparity, diabetes, hyperinsulinemia, and polycystic ovary syndrome (PCOS). Metformin use appears to reduce the risk of endometrial cancer.
4. **FERTILITY ASSESSMENT:** Before deciding whether a patient is suitable for FST, it is crucial to assess their fertility and her likelihood of becoming pregnant. Any patient considered for FST should be referred to a fertility specialist for an evaluation of their fertility potential, including ovarian reserve markers like anti-Müllerian hormone levels and antral follicle count. Additionally, semen analysis should be performed on the partner. If the patient is obese, weight loss should be recommended.
5. **SURGICAL TREATMENT:** The most effective fertility-sparing approach involves a combination of hysteroscopic resection followed by oral and/or intrauterine progestin therapy, with the highest success rates for complete response and live birth.
  - **Focal lesions:** For focal lesions, tumor resection should follow the “three-step” Mazzone technique,<sup>3</sup> which includes the removal of the exophytic tumor, the adjacent endometrium (4–5 mm beyond the lesion), and the underlying myometrium (3–4 mm below the lesion).
  - **Diffuse atypical endometrial hyperplasia:** In cases of diffuse atypical endometrial hyperplasia, hysteroscopic endometrial resection should be performed using a tissue removal device (TRD).<sup>4</sup> The use of TRD reduces the risk of electrosurgical complications, such as the formation of postoperative intrauterine adhesions.
  - **Diffuse endometrial cancer:** In selected cases of diffuse endometrial cancer, a combined hysteroscopic resection<sup>5</sup> is recommended. A 15 Fr bipolar miniresectoscope is used to remove the main lesions following the Mazzone “three-step” technique, and a TRD should be used to complete the resection in difficult areas, such as the tubal ostia.
6. **IMMUNOHISTOCHEMICAL ASSESSMENT:** Immunohistochemistry to identify mismatch repair-deficient (MMR-d) tumors is required for identifying patients at high risk for Lynch syndrome. In the case of MMR-d tumors, genetic counseling is advised. If Lynch syndrome is confirmed, patients should receive counseling regarding the risk of developing additional cancers and of the potentially worse prognosis of FST. In patients presenting p53 aberrant phenotype tumors, FST would be inappropriate.<sup>1</sup>
7. **HORMONAL THERAPY:** Progestin therapy should be initiated immediately after hysteroscopic tumor resection.
  - **Grade 1 endometrioid endometrial cancer:** In cases of grade 1 endometrioid endometrial cancer, intrauterine progestin and/or oral progestin should be considered. Oral regimens include megestrol acetate 160 mg daily (either 40 mg orally four times a day or 80 mg orally twice daily) or medroxyprogesterone acetate 600 mg daily.
  - **Grade 2 endometrioid endometrial cancer:** In cases of grade 2 endometrioid endometrial cancer, the combined use of oral and intrauterine progestins might improve the complete remission rate.<sup>6</sup> This combined approach should also be considered for MMR-d tumors, especially if the patient wishes to continue FST.
8. **FOLLOW UP:** Two consecutive endometrial biopsies showing complete response (CR) with a minimum interval of 3 months are necessary to confirm the success of FST and to recommend pregnancy. The recommended duration of therapy is 6–12 months, during which CR should be achieved. The maximum time to achieve CR should not exceed 15 months. Once CR is achieved, follow-up with maintenance progestin therapy should continue until pregnancy is planned. If CR is confirmed, biopsies should be performed every 3–6 months until pregnancy occurs or definitive surgery is carried out. Due to the frequent follow-up required, patient cooperation is essential for early detection of CR or relapse. Women who have been on progestin therapy for at least 6 months and have had two consecutive negative biopsies should be encouraged to stop therapy and attempt to conceive.
9. **FERTILITY TREATMENT:** Many young women with endometrial cancer also have PCOS and might experience amenorrhea or oligomenorrhea. Therefore, natural conception might be challenging even after achieving CR. For these patients, assisted reproductive technology should be considered, and they should be promptly referred to a fertility clinic.
10. **DELIVERY:** There are no specific guidelines for delivery after FST. Childbirth can occur spontaneously, except in cases of pregnancy-related complications.
11. **DEFINITIVE SURGERY:** Definitive surgery is recommended after childbearing is complete. Completion surgery is recommended for patients who are non-responders, unable to conceive, experience recurrence, or show disease progression. For patients with a strong desire to preserve fertility, a second round of FST can be considered on a case-by-case basis.

## AUTHOR CONTRIBUTIONS

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## CONFLICT OF INTEREST STATEMENT

We, the authors, declare that we have no conflicts of interest related to the research presented in this manuscript. We confirm that there are no financial, personal, or professional relationships that could be perceived to influence the work.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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