Fertility-Sparing Treatment in Young Women Diagnosed with Endometrial Cancer: Review of Safety, Pregnancy Outcomes, and Current Recommendations

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Semin Reprod Med

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Abstract

With the rising incidence of endometrial cancer, including among young women, and the trend of increasing age among first-time mothers, the need for safe and effective fertility-sparing treatments for endometrial cancer and atypical endometrial hyperplasia has become crucial. Focusing on studies from the past decade, this review synthesizes findings on the safety and outcomes of fertility-sparing treatments for endometrial cancer and atypical endometrial hyperplasia and provides an overview of current treatment recommendations. Fertility-sparing treatment, including hysteroscopic tumor resection followed by hormonal therapy with oral progestins and/or the insertion of a levonorgestrel-releasing intrauterine device, can be offered to a selected group of women of reproductive age who wish to preserve their ability to become pregnant in the future. The safety of conservative treatment for women diagnosed with Stage 1A, Grade 1 endometrial cancer without myometrial invasion is high; however, current evidence on the safety of this treatment for women with Grade 1, Stage 2 endometrial cancer is limited. Even though the success rate in terms of pregnancies and deliveries is high, it is not as high as in the general population, and women should be informed of the potential need for assisted reproductive technology.

Keywords

- assisted reproductive technology
- atypical endometrial hyperplasia
- endometrial cancer
- fertility preservation

Endometrial cancer is the sixth most common cancer in women worldwide, with an incidence of 420,242 new cases in 2022.[1] The incidence of endometrial cancer has been rising over the past few decades, and although the total number of women diagnosed with endometrial cancer in reproductive age is still relatively low, the growing incidence, particularly among younger women, is becoming an increasing concern.[2] Standard treatment for endometrial cancer involves total hysterectomy, often combined with bilateral salpingo-oophorectomy, which is a significant concern for young women who may not have started or completed their desired family. The problem is further substantiated by the trend of increasing age of first-time mothers. While the focus of most oncologists is (and should be) to offer the patient a life-saving treatment, there are nevertheless cases in which pregnancy wish can be taken into consideration. Increasing focus is now given to fertility-sparing treatment of young women diagnosed with endometrial cancer in selected cases. This review offers an overview of current recommendations and associated outcomes of fertility-sparing management of endometrial cancer and atypical endometrial hyperplasia.

Background—Etiology and Risk Factors of Endometrial Cancer in Women of Reproductive Age

In premenopausal women, a hormonal imbalance, characterized by excess estrogen relative to insufficient

Issue Theme Gynecological Cancers; Guest Editor, Kirsten Tryde-Macklon, MD

Thieme Medical Publishers, Inc., 333 Seventh Avenue, 18th Floor, New York, NY 10001, USA

DOI https://doi.org/10.1055/s-0045-1809041.
ISSN 1526-8004.

progesterone, is the primary risk factor for endometrial cancer. Increased levels of estrogen, and the resulting continuous stimulation of the endometrial lining, can lead to endometrial hyperplasia and possibly endometrial cancer. In women of reproductive age, risk factors for endometrial cancer include irregular menstrual cycles, high body mass index (BMI), insulin resistance and a mitogenic effect of insulin, and nulliparity, among others.[3–5] These are all factors associated with increased estrogen levels. During a normal menstrual cycle, the endometrium thickens in response to the increasing amount of estrogen produced by growing follicles in the follicular phase. After ovulation, the corpus luteum, in addition to estrogen, produces progesterone, which stabilizes the endometrium and prepares it for possible implantation. In the absence of pregnancy, the corpus luteum degenerates after approximately 13 days. In response to the sudden drop in estrogen and progesterone, the endometrium is shed during menstruation. In irregular non-ovulatory cycles, progesterone is not produced. Consequently, prolonged estrogen exposure without shedding causes the endometrial lining to thicken, increasing the risk of abnormal cell growth, possibly causing hyperplasia or cancer.

Fat tissue contains the enzyme aromatase, which converts androgens to estrogen. Therefore, an increase in fat tissue in obese women leads to higher levels of free circulating estrogen. Obesity is also associated with an increased risk of polycystic ovarian syndrome (PCOS), which is an endocrine disorder among women of reproductive age characterized by irregular or absent menstrual cycles, and the presence of multiple small cysts on the ovaries. PCOS is associated with an increased rate of endometrial cancer due to prolonged exposure to unopposed estrogen.[6]

Which Patients Are Eligible for Fertility-Preserving Treatment?

Assessment of Reproductive Potential

Women of reproductive age diagnosed with early-stage, nonmetastatic grade 1 endometrial cancer or atypical endometrial hyperplasia who wish to obtain pregnancy should be considered for fertility-sparing treatment. In addition to age, which is the most important indicator of reproductive potential in women, anti-Müllerian hormone (AMH), antral follicle count (AFC), and day 2–5 follicle-stimulating hormone (FSH) levels are primary indicators used to evaluate the reproductive potential in women of reproductive age. To the best of our knowledge, no literature specifically covers the assessment of reproductive potential in premenopausal women diagnosed with endometrial cancer. As a result, the primary indicators of fertility mentioned earlier are also applied to this patient group. Overweight and obesity have a negative impact on fertility and are possibly associated with weak adverse outcomes among women undergoing in vitro fertilization.[7,8] However, a randomized controlled trial (RCT) in overweight patients with a BMI between 30 and 35 randomized to either receive a reduced caloric intake before IVF or go straight to IVF did not demonstrate a positive benefit in the weight loss group.[9] The negative impact of obesity on fertility rates is also found among obese patients treated with fertility-sparing surgery for atypical endometrial hyperplasia and endometrial cancer.[10,11] Therefore, emphasizing the importance of weight loss and maintaining a healthy weight is crucial, also for this patient group, to improve overall health outcomes and possibly the future chances of obtaining pregnancy.

We recommend that before the decision to offer fertility-sparing treatment is made, a comprehensive medical history should be obtained. This includes details of previous fertility treatments and attempts, history of miscarriages, age, BMI, bleeding disorders, and comorbidities, such as PCOS. In cases involving ovarian cysts, hormonal status and ovarian cancer markers, both epithelial and nonepithelial, are also assessed. Patients with a high BMI should be encouraged to adopt a healthy lifestyle in collaboration with a dietitian to promote weight loss and possibly improve fertility chances.

Should Fertility-Preserving Treatment Be Offered to Patients with Lynch Syndrome?

Lynch syndrome, previously known as hereditary non-polyposis colorectal cancer (HNPCC), is a genetic disorder with a prevalence of 0.9 to 2.7%.[12] Lynch syndrome increases the risk of developing colorectal cancer, ovarian cancer, and endometrial cancer. The lifetime risk of developing endometrial cancer for patients with Lynch syndrome is 60%.[13] Patients with Lynch syndrome who are diagnosed with endometrial cancer are often diagnosed at a younger age and typically at an early stage of the disease.[14] The question of whether this patient group should be offered fertility-sparing treatment is therefore highly relevant. Data on relapse rates for women with Lynch syndrome and endometrial cancer undergoing fertility-sparing surgery are scarce and largely based on small case studies. Therefore, little evidence exists on the safety of fertility-sparing treatment for women with endometrial cancer and Lynch syndrome. To avoid transmitting the genetic disorder to the next generation, women with Lynch syndrome may be offered preimplantation genetic testing for monogenic/single-gene disorders (PGT-M), which can ensure that the gene is not passed on to their offspring.[15] However, this procedure may require several attempts at creating healthy embryos and may further prolong the time to pregnancy. While PGT-M is increasingly offered to women carrying BRCA gene mutations, it is still not offered as frequently to women with Lynch syndrome. Furthermore, when considering fertility-sparing treatment for women with Lynch syndrome and endometrial cancer, the risk of synchronous ovarian cancer should also be assessed and ruled out.[12] The lifetime risks of colon and ovarian cancer in Lynch syndrome compared to the general population are reported to be 43 to 48% and 5.8 to 10.3% vs. 5.5 and 1.4%, respectively.[12]

Tumor Characteristics

Fertility-sparing treatment for endometrial cancer and atypical endometrial hyperplasia should be considered only for women presenting with early-stage nonmetastatic disease.

Although patients with Stage 1A Grade 1 endometrial cancer without myometrial invasion have proven a great response to progestin and a low to moderate risk of recurrence,[16–18] the evidence of conservative treatment for Stage 1A Grade 2 endometrial cancer is scarce. In a prospective study, 23 patients diagnosed with stage 1A Grade 2 endometroid cancer were treated with hysteroscopic resection and progestin. The median follow-up time was 35 months, and 17 patients (74%) showed a complete response. The recurrence rate was 41%.[19] A retrospective study found that seven out of eight patients treated conservatively for stage 1A Grade 2 endometrial adenocarcinoma achieved complete response. Three patients experienced a recurrence, and two of the three patients achieved a complete response after second-line fertility-sparing treatment. The average follow-up time was 31 months.[20] Hwang et al performed a study to assess the oncologic outcomes of combined oral medroxyprogesterone acetate/levonorgestrel-intrauterine system treatment in young women with grade 2-differentiated stage 1A endometrial adenocarcinoma who wanted to preserve fertility. All patients received treatment with combined oral MPA (500 mg/day)/levonorgestrel-releasing intrauterine device (LNG-IUD) and curettage every 3 months, with an average follow-up duration of 44 months. Three of five patients achieved a complete response, while the remaining two patients achieved a partial response. One patient achieved recurrence after 14 months.[21] In summary, evidence supporting fertility-sparing treatment for women diagnosed with Stage 1A Grade 2 endometrial cancer remains limited. Consequently, fertility-sparing options should be carefully considered and discussed on a case-by-case basis.

Establishment of a Reliable Histopathology

To ensure the safety of fertility-sparing treatments, accurate diagnostic methods are essential. An endometrial biopsy is the primary diagnostic procedure for detecting and staging endometrial cancer. Hysteroscopic-guided endometrial biopsy is widely regarded as the gold standard. A meta-analysis of 56 studies assessed the accuracy of hysteroscopy in diagnosing endometrial cancer and hyperplasia. The study found a sensitivity of 86.4% (95% CI, 84.0–88.6%) and a specificity of 99.2% (95% CI, 99.1–99.3%).[22] Another meta-analysis of four studies, including a total of 1,295 patients, compared sample adequacy, failure rates in detecting endometrial cancer or hyperplasia, and the detection rates of endometrial cancer between endometrial biopsy conducted under direct hysteroscopic visualization and blind sampling. The study found that an endometrial biopsy conducted under direct hysteroscopic visualization was significantly more likely to provide an adequate sample (RR: 1.13, 95% CI: 1.10–1.17) and posed a reduced risk of missing endometrial cancer or hyperplasia (RR: 0.16, 95% CI: 0.03–0.92) compared to blind endometrial sampling.[23]

Assessment of Myometrial Invasion and Exclusion of Metastatic Disease/Synchronous Cancer

To date, studies evaluating the accuracy of transvaginal ultrasound (TVUS) and magnetic resonance imaging (MRI) in detecting myometrial invasion in women with endometrial cancer have aimed at focusing on the accuracy of diagnosing deep myometrial invasion (>50% invasion of the myometrium). A meta-analysis including eight studies found no statistically significant difference between using TVUS and MRI in detecting deep myometrial invasion. Sensitivity and specificity for detecting deep myometrial invasion were 75% (95% CI: 67–82%) and 82% (95% CI: 75–93%) for TVUS and 83% (95% CI: 76–89%) and 82% (95% CI: 72–89%) for MRI, respectively,[24] and similar results are found in other studies.[25] To the best of our knowledge, no studies have specifically investigated the accuracy of detecting shallow myometrial invasion (< 50% invasion of the myometrium). Although metastatic disease is rare, it still poses a challenge and should be ruled out in all women diagnosed with endometrial cancer, particularly those opting for fertility-sparing treatment. This can be achieved through ultrasound (US), computed tomography (CT) scanning, positron emission tomography (PET)-CT, or MRI, depending on the availability and individual patient characteristics.[26,27]

Treatment Protocol

Fertility-sparing treatment for endometrial cancer and atypical endometrial hyperplasia consists of hysteroscopic tumor resection in case of localized disease, followed by hormonal treatment with oral progestins and/or the insertion of an LNG-IUD.[27] Most commonly, medroxyprogesterone acetate or megestrol acetate is used as an oral progestin. The recommended dose for medroxyprogesterone acetate is 400 to 600 mg/day, while for megestrol acetate, it is 160 to 320 mg/day.[28] Patients are typically monitored through a comprehensive surveillance program, which includes TVUS, hysteroscopy with biopsy, and/or curettage every third month.[29] Complete response is expected within 6 to 12 months.[30] Providing detailed information about the treatment plan is necessary. Additionally, a discussion should address the potential discontinuation of conservative treatment by either the patient or the physician, for example, in cases of partial or no response, or if the patient no longer wishes to proceed with conservative treatment. Furthermore, it is important to underline the standard treatment, which includes total hysterectomy and removal of the tubes. Normal ovaries may be preserved, as there is no evidence on whether this is associated with a significant adverse impact on survival.[28]

Outcomes

Oncological Treatment Outcomes

Fertility-sparing surgery, including hysteroscopic resection followed by hormonal treatment, for patients with atypical endometrial hyperplasia or endometrial cancer is associated with promising oncological outcomes, as reported in the literature. ►**Table 1** summarizes representative and updated systematic reviews and meta-analyses on oncological and obstetric outcomes in women of reproductive age who received conservative treatment for endometrial cancer

Table 1 Representative updated systematic review and meta-analyses on the oncological and obstetric outcomes for women of reproductive age conservatively treated for endometrial cancer and atypical hyperplasia

Publication	Patients, *n*	Stage of disease	Treatment protocol	Complete response, % (95% CI)	Recurrence, % (95% CI)	Pregnancies %, (95% CI)	Live births %, (95% CI)
Zhao et al[35]	851 (AH = 444, EC = 407)	1A, low- or intermediate-grade EC and AH	HR + either: oPG, LNG-IUS, GnRH, or a combination	AH = 97.0 [94.7; 98.8] EC = 88.6 [84.8; 92.0]	AH = 10.8 [4.6; 18.6] EC = 18.3 [13.7; 23.3]	EC = 32.4 [20.2; 45.9]	AH = 22.2 [10.8; 35.8] EC = 26.0 [17.3; 35.5]
Herrera Cappelletti et al[34]	861	1A, well-differentiated endometrioid EC	Various treatment protocols including oPG, IM PG, LNG-IUD, HR, GnRH agonist, AI in combination, or alone	79.9	35.3	26.7 [21.3; 32.3]	20.5 [15.7; 25.8]
Lucchini et al[31]	661	EC G1/2 and AH	HR + oPG/LNG-IUD oPG LNG-IUD	HR + oPG/ LNG-IUD = 90 oPG = 77.7 LNG-IUD = 71.3	HR + OPG/ LNG-IUD = 6.93 oPG = 29.17 LNG-IUD = 27.03	HR + oPG/ LNG-IUD = 34.5 oPG = 27.6 LNG-IUD = 18.4	
Wei et al[36]	1,038	AH and early EC (not further specified)	oPG LNG-IUD oPG + LNG-IUD	oPG = 71 [63; 77] LNG-IUD = 76 [67; 83] oPG + LNG-IUD = 87 [75; 93]	oPG = 20 [19; 40) LNG-IUD = 9 [5; 17]	oPG = 34 [30; 38] LNG-IUD = 18 [7; 37] oPG + LNG-IUD = 40 [20; 63]	oPG = 20 LNG-IUD = 14 oPG + LNG-IUD = 35
Zhang et al[37]	Not specified (54 studies)	EC G1 or AH	HR +/− oPG oPG LNG-IUD	HR +/− oPG = 98.06 [90.32; 100.00] oPG = 77.20 [72.58; 81.51] LNG-IUD = 94.24 [83.23; 99.60]	HR +/− oPG = 4.79 [0.16; 15.23] oPG = 32.17 [25.06; 39.71] LNG-IUD = 3.90 [0.08; 12.98]		HR +/− oPG = 52.57 [24.66; 79.64] oPG = 33.38 [26.70; 40.42] LNG-IUD = 18.09 [7.42; 32.14]

Abbreviations: AH, atypical hyperplasia; AI, aromatase inhibitors; EC, endometrial cancer; GnRH, gonadotropin-releasing hormone; HR, hysteroscopic resection; IM PG, intramuscular progestin; LNG-IUD, levonorgestrel intrauterine device; oPG, oral progestin.

and atypical hyperplasia. A systematic review and meta-analysis of 38 studies involving 661 patients revealed an overall complete response rate of 90% for hysteroscopic resection followed by progestin therapy. In comparison, response rates were 77.7 and 71.3% for treatment with either oral progesterone or the LNG-IUD alone, respectively.[31] Furthermore, patients who underwent tumor resection had a lower rate of progression compared to those who received either oral progestin or an LNG-IUD alone (3.5% vs. 12.1 and 19.5%, respectively, $p = 0.03$).[31] A prospective study by Falcone et al. including 28 endometrial cancer patients conservatively treated with hysteroscopic resection, followed by either oral megestrol acetate or the insertion of an LNG-IUD, found that 25 patients (89.3%) achieved complete regression 3 months after progestin initiation. Of the 25 patients, two experienced a recurrence.[32] These findings are supported by other studies.[30,33]

Pregnancy Outcomes

A systematic review and meta-analysis including 861 patients found that women undergoing progestin-based conservative management for endometrial cancer had a 26.7% (95% CI: 21.3–32.3%) likelihood of achieving pregnancy and a 20.5% (95% CI: 15.7–25.8%) likelihood of a live birth.[34] A 2024 meta-analysis of 21 studies, including 407 patients with low- or intermediate-grade endometroid endometrial cancer and 444 patients with atypical endometrial hyperplasia, reported pregnancy and life birth rates of 32.4% (95% CI: 20.2%;45.9%) and 26.0% (95% CI: 17.3%;35.5%), respectively, for patients with endometrial cancer. The live birth rates for patients diagnosed with atypical endometrial hyperplasia were 22.2% (95% CI: 10.8–35.8%).[35] The study also found that a higher BMI (>28) was linked to lower clinical pregnancy and live birth rates. Specifically, individuals with a higher BMI had clinical pregnancy and live birth rates of 28.4 and 23.0%, respectively, compared to 32.9 and 31.1% in those with lower BMI.[35] Studies indicate that pregnancy rates are higher for women treated with oral progestin or a combination of oral progestin and an LNG-IUD compared to LNG-IUD alone.[35,36] Additionally, hysteroscopic resection followed by hormonal treatment is superior to hormonal treatment alone in terms of live birth rates.[34,37] These findings are summarized in ►**Table 1**.

Use of Assisted Reproductive Technology

Studies comparing the likelihood of pregnancy through natural conception versus fertility treatment in fertile women conservatively treated for endometrial cancer are currently lacking. Although natural conception may be attempted in young women with no known history of infertility or risk factors, most clinicians recommend referral to ART when trying to conceive, particularly if the woman is over 35 years of age, to shorten the time to pregnancy. However, trying for a spontaneous conception can be allowed, at least for a limited period of time.[27] To better identify patients who may need ART, a fertility assessment by a fertility specialist is recommended at the time of diagnosis, including a semen analysis of the partner. If severe fertility obstacles are encountered, the patient may not even be a candidate for fertility-sparing surgery. Ovarian stimulation with high-dose gonadotrophins will inevitably lead to increased serum estradiol concentrations, which, at least in theory, may negatively interact with the endometrial cancer diagnosis. To circumvent this, cotreatment with letrozole, an aromatase inhibitor, is recommended.[38] The literature does not provide a "safe" threshold of a number of ART attempts to offer the patient, nor how much time is allowed to try for a pregnancy before resumption of conservative treatment or definitive surgical treatment is recommended. A prospective study found a live birth rate of 34% in 88 women with stage 1A endometrial cancer or endometrial hyperplasia using ART to conceive, a number that equals that in a standard infertility population using ART.[39] However, at present, it is unknown whether the multiple endometrial biopsies needed in the conservative management of early endometrial cancer or hyperplasia will negatively affect the endometrium's ability to allow implantation and the support of an early pregnancy.

The Use of Bariatric Surgery

In addition to dietary and lifestyle changes, bariatric surgery is increasingly used for weight loss, including among women of reproductive age. A 2024 systematic review and meta-analysis found that bariatric surgery significantly reduced infertility, with an RR of 0.55 (95% CI: 0.06–0.74, $p = 0.00001$).[40] However, obstetrical outcomes following bariatric surgery are reported as conflicting in the literature. A systematic review and meta-analysis from 2018 found that patients who underwent bariatric surgery showed decreased rates of gestational diabetes mellitus (OR: 0.20, 95% CI: 0.11–0.37), large-for-gestational-age infants (OR: 0.31, 95% CI: 0.17–0.59), gestational hypertension (OR: 0.38, 95% CI: 0.27–0.53), and caesarean section (OR: 0.05, 95% CI: 0.38–0.67). The same study found that the procedure increased the risk of small-for-gestational age infants (OR: 2.16, 95% CI: 1.34–3.48), intrauterine growth restriction (OR: 2.16, 95% CI: 1.34–3.48), and preterm deliveries (OR: 1.35, 95% CI: 1.02–1.79) when compared with women matched on preoperative BMI.[41] Due to accelerated weight loss and possible malnutrition following bariatric surgery, women are advised to avoid pregnancy for 12 to 18 months after the procedure.[42] This may pose a challenge for women conservatively treated for endometrial cancer, who are recommended to become pregnant immediately after complete response has been obtained. Also, age is the most important factor in fertility, so this delay, especially among women of advanced maternal age, must also be carefully considered when evaluating bariatric surgery for women with endometrial cancer or atypical endometrial hyperplasia who wish to preserve future fertility.

Recurrence Rates and Definitive Surgery Following Pregnancy

Due to the high recurrence rate, total hysterectomy, with or without bilateral salpingo-oophorectomy, is generally recommended after delivery. A prospective study found that out of 50 patients with endometrial carcinoma or atypical

endometrial hyperplasia who achieved complete regression through conservative treatment, 17 (34%) experienced a recurrence. Sixteen patients underwent hysterectomy, and of 11 patients with no preoperative abnormalities, 4 were diagnosed with atypical endometrial hyperplasia postoperatively, indicating a high rate of undetected recurrence.[43] A systematic review and meta-analysis including 100 patients across 10 studies found that 17.2% experienced recurrence after 12 months, and 29.2% experienced recurrence after 24 months.[44] In a meta-analysis, Qin et al. reported a comparable high relapse rate of 25.0% (95% CI, 15.8–35.2).[45] The high recurrence rates observed in women treated with fertility-sparing therapy underscore the severity of the disease and highlight the critical need for close monitoring at centralized, highly specialized centers. For women who do not respond to fertility-sparing treatment within 6 to 12 months or who experience progression of disease, hysterectomy is also recommended (►**Table 1**).[28]

What Should Be Recommended for Those Who Do Not Get Pregnant Immediately or Those Who Want a Second Pregnancy?

Recommendation on how long to allow for a pregnancy after complete response has been obtained will most likely vary from clinic to clinic and from patient to patient. No evidence exists regarding when it is no longer considered safe to attempt pregnancy. Therefore, each case must be carefully discussed with the patient, weighing risks against benefits. Likewise, the usual recommendation is to proceed with definitive surgery following delivery for patients who achieve pregnancy. However, in cases where the patient strongly desires a second pregnancy, close surveillance and maintenance treatment with an LNG-IUD should be offered if deemed safe.

Conclusion

Fertility-sparing treatment can be offered to a selected group of women of fertile age with early-stage, nonmetastatic grade 1 endometrial cancer or atypical endometrial hyperplasia, who want to obtain pregnancy. The safety of conservative treatment for women diagnosed with stage 1A, grade 1 endometrial cancer without myometrial invasion is high. However, current evidence on the safety of this treatment for women with grade 1, stage 2 endometrial cancer is limited. Consequently, fertility-preserving options for this patient group should be carefully considered and discussed individually. The treatment is hysteroscopic tumor resection followed by hormonal treatment with oral progestins and/or the insertion of an LNG-IUD. Once a complete response has been achieved, the patient should attempt pregnancy immediately. The success rates in terms of pregnancies and live births are high, although not as high as for the general population even with IVF. Several factors may contribute to this, with obesity, PCOS, anovulation, and higher age—all associated with an increased risk of endometrial cancer and subfertility—playing a significant role. It is thus important that the patient is referred to a fertility specialist even before deciding on fertility-sparing treatment, and it may be necessary to perform ART once a complete response is achieved.

Conflict of Interest
None declared.

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