Fertility Preservation in Endometrial Cancer: Current Knowledge and Practice

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ABSTRACT

Uterine cancer affects more than 1.28 million people worldwide; considering current world trends in obesity and aging, a +52.7% growth by 2040 is foreseen. Around 5% of endometrial cancer patients are less than 40 years old, meaning that conventional oncologic approaches would result in fertility loss; thus, it is essential to consult patients regarding their fertility and family planning.

Owing to developments of oncofertility, patients are now able to preserve their fertility and complete their childbearing, drafting from the standard of care in endometrial cancer. Strict criteria should be applied to make sure of selecting patients who benefit most from the fertility preservation approach. Furthermore, careful selection of patients increases the possibility of successful treatment.

Most candidates for fertility preservation have risk factors in common with infertility, including polycystic ovarian syndrome, obesity, increasing of age and irregular menses; therefore, Advanced Reproductive Technology (ART) can improve their chances for pregnancy.

Current applied knowledge towards the fertility preservation approach in patients with endometrial cancer is reviewed in this article.

Keywords: Endometrial Cancer, Fertility Preservation, Oncology, Gynecology, Oncofertility

Introduction

Uterine cancer is the commonest gynecological cancer in high-income countries and the second most common cancer after cervical cancer in developing countries, affecting more than 1.28 million people worldwide, with an increasing incidence rate of 382,069 per year that is estimated to reach as high as 583,560 (52.7% growth) by 2040 (1, 2). Given the current world trends in obesity and aging (the most important risk factors of endometrial cancer alongside genetics) in the increasing incidence of endometrial cancer is repeatedly considered (3-9). Around 14%-25% of endometrial cancer patients are premenopausal, and about 5% of patients are less than 40 years old, of whom 70% of cases are nulliparous (10-13). Aging, delayed childbearing, and polycystic ovarian syndrome affect fertility and susceptibility to endometrial cancers (11, 14-17). Other risk factors include hyperinsulinemia, type 2 diabetes, hypertension, early menarche, late menopause, sedentary lifestyle, nulliparity, and Lynch syndrome (10, 13, 18, 19).

Fertility-sparing treatment was first introduced by Kistner in 1959 as case series of 6 patients who responded to progestin therapy with different doses and formulations (20). The current standard of care in endometrial cancer patients is comprised of total hysterectomy and bilateral salpingo-oophorectomy (TH+BSO) and staging, leading to infertility (11, 14-16, 21). Therefore, it is essential to consult patients regarding their fertility and family planning, as studies suggest that fewer patients are likely to regret their decision if consulted thoroughly (15, 16, 18).

BSO is part of standard treatment; however, the aforementioned procedure has a significant impact on the patient’s quality of life, leaving both short- and long-term sequelae, e.g., Alzheimer’s disease, osteopenia, early post-menopausal symptoms, and increased cardiovascular risk. The overall decrease in quality of life and all-cause mortality are higher in these patients (91.3% compared to 94.5% in overall survival) (22-24).

Cytotoxic chemotherapy, pelvic radiation, and hysterectomy as standard procedures have improved oncological outcomes. On the other hand, these
approaches lead to severe deterioration of fertility outcomes (11, 14-16, 18, 21).

The psychological burden changes significantly with the fertility outcome, as it is almost comparable to the diagnosis of malignancy itself (15). Accordingly, experts emphasize patient education regarding fertility preferences before the treatment begins (11, 15, 18, 21, 25). Also, endometrial cancer and infertility have many risk factors in common, such as obesity, chronic anovulation, and polycystic ovary syndrome (PCOS). Therefore, patients benefit most from a multidisciplinary team involving reproductive endocrinologists/infertility specialists, gynecology oncologists, radiation oncologists, and psychologists (15, 19).

**Fertility and Reproductive Techniques**

Emerging techniques in embryology grant candidates a chance to conceive. Around 5% of endometrial cancer patients are less than 40 years old; therefore, fertility preservation is of particular importance. In addition, patients receiving standard treatment have a good prognosis, as the 5-year-survival rate after surgery for early-stage endometrial cancer is reported to be over 93% (26). Following the diagnosis, patients should be referred to an infertility center as soon as possible to consult with an experienced oncofertility specialist. Factors determining the most appropriate method for fertility preservation are age, health status, previous fertility history, planning of treatment, and available time to initiate cancer treatment (15). If a delay in surgery of 2 to 6 weeks is acceptable, cryopreservation of oocyte and/or embryo is a standard method for fertility preservation in candidates for surgery. Accordingly, these patients are candidates for in vitro fertilization (IVF) following controlled ovarian stimulation (27, 28).

Measuring ovarian reserve is the first step to assess fertility potential. Anti-Müllerian hormone (AMH) and antral follicle count are commonly used to predict the response to ovarian stimulation, even though they do not determine the likelihood of pregnancy. Above all, age is the main factor to predict the ultimate success of fertility preservation; thus, despite acceptable ovarian reserve, older age is associated with a decreased success of fertility preservation. Studies show that the live birth rate with cryopreserved oocytes for women without cancer at ages 25 and 30 is around 53% and 32%, respectively (15).

The ovarian stimulation protocol is generally selected according to the policies of each health center, and the early initiation of cancer treatment is of crucial and decisive importance. Today, it is possible to stimulate the ovaries regardless of a patient’s menstrual cycle phase and can be started on any day of the menstrual cycle, even in 2 phases. In cancer patients, ovarian stimulation using a gonadotropin-releasing hormone (GnRH)-antagonist is the recommended protocol because less time is needed (29). The potential risk of supraphysiological levels of estradiol is one of the major concerns about controlled ovarian stimulation protocols. Concomitant development of multiple follicles following administration of gonadotropins may exacerbate the oncological outcomes in estrogen-sensitive cancers, including endometrial cancer. Safer ovarian stimulation protocols are executed using anti-estrogenic drugs alone or in combination with lower doses of gonadotropins, which are associated with comparable results to the standard protocols (30).

Potentially safe protocols for ovarian stimulation include natural-cycle IVF (without ovarian stimulation), stimulation protocols with tamoxifen or aromatase inhibitors alone or combined with gonadotropins to decrease the estrogen level. Due to the limited number of oocytes or embryos (1-2 per cycle) and the high rate of cancellation, the use of natural IVF cycles is not often recommended. According to studies, tamoxifen is also commonly used in patients with estrogen receptor (ER)-positive breast cancer, but it is often recommended to use letrozole as an aromatase inhibitor for patients with endometrial cancer. Studies have indicated that controlled ovarian stimulation protocols with letrozole in endometrial cancer patients are successfully used for cryopreservation of oocytes or embryos.

In estrogen-sensitive cancers, the major benefit of letrozole adding to gonadotropins is the reduction in estradiol levels without affecting the number and quality of the oocytes. Letrozole results in greater oocyte counts and higher fertility rates. Thus, letrozole-induced ovarian stimulation protocols are preferred over protocols with tamoxifen administration. Depending on the patient’s ovarian reserve, letrozole is administered at a dose of 2.5 to 5 mg daily in ovarian stimulation cycles. It is recommended that serum estradiol concentrations be monitored throughout the cycle. Administration of letrozole should be continued until post-ovulation when the serum concentration reaches below 500 pg/mL. Based on available evidence, the recommended dose of gonadotropin for ovarian stimulation is 150 IU/d for cancer patients, especially those sensitive to estrogen (29).

In a retrospective study of 74 patients with early-stage endometrioid endometrial cancer (EEC) and 23 patients with atypical endometrial hyperplasia (AEH) who underwent fertility-sparing treatment, the rate of the good quality embryo was higher in the progestin primed ovarian stimulation (PPOS) group (20 mg/d oral dydrogesterone and 150 to 300 IU/d human menopausal gonadotropin [hMG] from day 2-3 of the menstrual cycle) than in the standard regimen group, including short agonist regimen and antagonist regimen ($P=0.034$; $P=0.034$) (31).
Typing

Historically, the American College of Obstetrics and Gynecology (ACOG) classified all endometrial cancers into 2 large subgroups (9, 32):

1- Type 1: Histology of endometrioid adenocarcinoma accounts for 85% of ECs, and 75% are low-grade and diagnosed at an early stage.

2- Type 2: More aggressive histology with less favorable outcomes (including clear cell carcinoma and papillary serous carcinoma, undifferentiated carcinomas, mixed cell, and carcinosarcoma), although rare, account for more than 40% of deaths due to endometrial cancer. The risk of extrauterine disease is higher in this group, and patients are more likely to be diagnosed at advanced stages.

New classification systems based on molecular typing have been developed to provide prognostic information and planning of adjuvant treatment (33):

1- Ultramutated/DNA polymerase epsilon group (POLE): Patients with POLEmut EC are often young with low body mass index (BMI) and have a very favorable prognosis, despite aggressive pathological features (e.g., high-grade, lymphovascular space invasion; >96% 5-year survival).

2- Hypermutated/microsatellite unstable: Studies on the status of microsatellite instability (MSI) in clinical outcomes in EC have had conflicting results, but most have reported adverse prognoses. On the other hand, increased sensitivity to radiation therapy in DNA mismatch repair (MMR)-deficient ECs has been shown in some studies and may explain more favorable results in patients with advanced disease. This group might not be considered appropriate candidates for progesterone therapy due to the low progesterone receptor (PR) and ER.

3- Copy number low group: This group is characterized by MMR-intact ECs with moderate mutational load and moderate to favorable outcomes. This group includes endometrioid neoplasms with ER and PR positive and high response rates to hormone therapy.

4- Copy number high group: Tumor protein 53 (TP53) mutations are most commonly observed (92%) and correlated with significantly poor outcomes (approximately 50% 5-year survival).

Molecular classification of endometrial cancer is changing the approach to diagnosis and management in women. Certain subtypes of POLE mutant tumors, wild-type p53/non-specific molecular profile (NSMP) tumors, and MMR-deficient tumors with low-risk characteristics can be considered low-risk for disease progression and might be candidates for fertility-sparing treatment (13).

Grading

The International Federation of Gynecology and Obstetrics (FIGO) updated FIGO grading for endometrial cancer in 2010 based on solid tumor growth rather than gland formation. Nuclear grading should also be performed. In cases of grading mismatch between nuclear and solid tumor growth, a higher grade is considered as the overall tumor grading. Histologic grades II and III are significantly correlated with higher failure rates in conservative therapy. Increased recurrences of endometrial cancer and higher rates of synchronous ovarian involvement are also reported (23, 34-36). Although there are case reports of conservative management in these patients, there are significantly lower cancer-related and overall survival rates following uterine preservation treatment (34, 35, 37).

Staging

About 70%-75% of endometrial cancers are diagnosed at stage I, having a good prognosis, and the 5-year-survival rate is 94%; thus, staging remains the most important factor for the prediction of oncological outcomes (18, 38).

Surgical Staging

A “comprehensive surgical staging,” including the removal of the uterus and adnexa, pelvic and paraaortic lymph node dissection, and the cytological evaluation of peritoneal washing, is the gold standard treatment for endometrial cancer (18, 32).

• Stage I is defined as the malignancy confined to the corpus of the uterine. It is then subdivided into 1A (without or less than 50% of myometrial invasion) and 1B (50% or more of the myometrial invasion).

• Stage II is considered by cervical stromal involvement. Note that the glandular involvement is no longer considered stage II--but rather stage I.

• Stage III is the local or regional spread of the tumor, further subdivided into IIIA (involvement of the uterine serosa and/or adnexa), IIIB (vaginal and/or parametrial involvement), IIIC (metastases to pelvic and/or para-aortic lymph nodes). IIIC1 is defined as pelvic lymph nodes involved, whereas IIIC2 is positive para-aortic lymph nodes with or without pelvic lymph nodes. Positive cytology should be reported separately without changing the stage.

• Stage IV is further subdivided as IVA (involvement of bladder or rectal mucosa) and
IVB (distant metastasis, e.g., intra-peritoneal or inguinal lymph nodes involvement).

Clinical Staging

To evaluate the histologic type and grade, a dilatation and curettage (D&C) sampling is recommended rather than Pipelle sampling, as Pipelle has limited sensitivity to focal lesions (19, 39, 40). In candidates for fertility preservation, a diagnosis of grade 2 or higher is of great importance. D&C is associated with better diagnostic performance in determining the grading and less residue in subsequent hysterectomy (41). Endometrial biopsy should be done via hysteroscopy based on the European Society of Gynaecological Oncology (ESGO)/European Society for Radiotherapy and Oncology (ESTRO)/European Society for Pathology (ESP) consensus. Hysteroscopy provides direct visualization of the endometrium; this would provide a chance to look for focal lesions and debulk the tumor to reduce the duration of the progestin therapy compared to D&C (33).

Hysteroscopic resection (HR) can also be used in patients who did not adequately respond in the first 3 months of treatment (19, 42-44). Although a higher rate of positive cytology is observed in patients undergoing HR, a meta-analysis of 2,944 patients with endometrial cancer revealed no significant difference in long-term prognosis (45). A 3-step approach is commonly used for HR, including 1) resection of the tumor, 2) resection of the adjacent endometrium, 3) and removal of the myometrium beneath the tumor (46).

In the next step, after confirmation of low-grade endometrioid EC with D&C, pelvic imaging should be performed to assess myometrial invasion. Evaluation of myometrial invasion can be performed via magnetic resonance imaging (MRI) or transvaginal ultrasonography (TVUS) (47, 48). Among contemporary modalities, MRI is shown to be slightly more sensitive than TVUS. No significant difference is observed between TVS and MRI (19, 49). TVUS, performed by experts in oncology gynecology, has diagnostic accuracy comparable to MRI to assess myometrial and cervical stromal invasion than general gynecologists (50). Ultimately, MRI can be used to assess lymph node necrosis as a sign of metastasis, cervical stromal invasion, or extraterine spread of the tumor (9, 19, 51).

Evaluation for synchronous involvement of ovaries is also essential, as it is present in 5%-25% of women of childbearing age. In Song et al.’s study, a 4.5% risk of coexisting ovarian cancer was reported. However, in women with low-risk disease (no myometrial invasion, grade 1 endometrioid histology, normal-lookig ovaries), no cases of ovarian cancer were diagnosed (52). Laparoscopic investigation with ovarian biopsy can be beneficial in this manner, as MRI and CA-125 marker have shown limited sensitivity (10, 18, 49, 53).

Patient Selection Criteria

The following characteristics are uniformly mentioned in the literature (15, 19, 39, 53-55):
- Patients younger than 40 years old usually have low-grade endometrial cancer and respond better to progesterone therapy.
- Histology of endometrioid adenocarcinoma.
- Grade I: It is suggested that consultation on fertility-sparing treatment in patients with grade 2 tumors without myometrial invasion should only be performed in highly experienced centers, as there is currently little evidence of safety in this area.
- Absent of myometrial invasion: In grade 1 endometrioid tumor confined to the endometrium, the risk of extraterine disease was negligible. Only the British Gynecological Cancer Society (BGCS) guidelines consider women with superficial myometrial invasion as potential candidates for fertility-sparing treatment.
- Careful ruling out of extraterine involvement using MRI, TVUS, or laparoscopic observation by an expert.
- Negative history of hereditary cancers, such as Lynch syndrome or hereditary non-polyposis colorectal cancer (HNPCC). Patients with immunohistochemistry (IHC) staining positive for PSM2, MSH2, MSH6, and MLH1 or high-MSI are not suitable for fertility preservation. Currently, the National Comprehensive Cancer Network (NCCN) guidelines for hereditary cancers recommend universal screening for Lynch syndrome in endometrial cancer, regardless of age at diagnosis. There is currently no strong evidence for the safety of fertility-sparing treatment in this population of women (15, 54).
- No contraindications regarding progesterone use.
- Informed consent: Fertility preservation is not the standard of care in these patients, and even after achieving complete remission, there is a recurrence rate of 24%-45%.
- It is also worthy of note that even low-grade tumors might be associated with extraterine involvement (56).

Fertility-Sparing Treatments

Progestin, as the main treatment for fertility-sparing management, is currently used in 3 formulations. The response rate is as high as 76%-82%. Recurrence rates are variable; 10.5% to 41 % is commonly reported (51, 53, 57-61). The optimal dose and duration of progesterone use have not been determined (62).
1- Medroxyprogesterone acetate (MPA) 200-800 mg/d (most commonly 400-600 mg/d)

2- Megestrol acetate (MA) 160-320 mg/d

In comparison, these 2 oral progestin therapies have shown no significant difference in the recurrence or remission rates in most articles (49). In a meta-analysis of a retrospective observational study involving 370 patients with AEsH or endometrial cancer, significant complete remission in MA compared with MPA was reported (63). However, 2 studies suggest better remission rates and fewer recurrences using MPA (51).

3- Levonorgestrel-releasing intrauterine device (LNG-IUD) releases 20 mcg/day of levonorgestrel locally. This method reduces the systemic side effects of progestin compared with oral treatments, including edema, weight gain, nausea, liver dysfunction, acne, breast discomfort, appetite change, and headache. IUDs can be used in combination with oral treatment (10, 51). Moreover, LNG-IUDs achieve better pathologic regression and fewer relapses (16, 19, 64). In the retrospective cohort study by Rosas et al., 25 of 28 patients (89.3%) who received levonorgestrel intrauterine devices experienced remission (61). According to the meta-analysis by Fan et al., a 75.5% complete response (CR) rate was reported regarding LNG-IUD combined with gonadotropin-releasing hormone agonists (65). Note that oral progestin can also be prescribed to patients with IUD to maximize the tissue response (51).

4- Superficial resection of the endometrium with hysteroscopy, followed by treatment with progesterone, can be considered in patients with primary endometrial cancer (66). Intrauterine pressure should be kept low during hysteroscopy to prevent malignant cell dissemination.

Gonadotropin-releasing hormones are also used in combination with resection of the endometrium. Goserelin at a dose of 3.6 mg can be used subcutaneously every month for 3 months. The concomitant ovarian tumor should be ruled out before starting GnRH agonists using laparoscopic exploration, followed by ovarian biopsy (10). In a pilot study included obese endometrial cancer patients with a regimen 3.75 mg GnRH agonist every 4 weeks and 2.5 mg oral aromatase inhibitor daily, a CR of 100% was reported, and the time to reach CR was 3-6 months (67).

Follow-Up

Three months after initiation of any progestosterone treatment, endometrial sampling should be obtained. Pipelle sampling is preferable to avoid extensive damage to the endometrium (10, 39, 51). LNG-IUDs can be left intact during endometrial sampling (9, 51). Continuous samples should be obtained every 3 months. Compared with the baseline D&C sample, 4 conditions might be present (10, 39):

1. CR: no neoplastic lesion
2. Partial response: down-staged lesion
3. Persistent disease: lesion with the same grade as the baseline
4. Progressive disease: lesion with a higher grade or myometrial invasion or extraterine lesion

Patients with complete remission should continue their current treatment for another 3 months until a second Pipelle sample confirms the complete remission; thereafter, patients are encouraged to proceed with the pregnancy. A maintenance regimen of MPA, MA, or LNG-IUD or a combination therapy might be used for patients who do not desire to be pregnant immediately, though the risk of recurrence is not to be neglected (51). For patients who have been successfully treated with progesterone and have completed fertility, there is no high-quality evidence regarding the need for hysterectomy. However, most experts suggest patients return to the standard treatment due to the potential risk of recurrence. The risk of recurrence is estimated to be around 40% even after successful conservative treatment (19, 49, 51).

After successful pregnancy and subsequent childbirth, Pipelle biopsies should be continued 3 months after delivery and regularly after that (10, 15, 39, 51). Risk factors promoting endometrial cancer are often persistent; thus, the risk of recurrence remains as high as 24%-40% even with CR to treatment (19, 51).

The median time to achieve CR is estimated to be 8 weeks to 9 months, but obese and non-ovulating patients may require treatment for longer (19, 51). Those who did not achieve adequate response after 3 months may benefit from a higher dose of progestosterone. They should be evaluated for treatment response in 3-month intervals (36, 51). These patients can also benefit from HR, increasing the effectiveness of hormonal treatment (19, 39, 53, 57). A complete regression rate of 96.3% is reported when 3-step HR was added to oral progestins compared with 78% when oral progestins were used alone. HR also reduces recurrence rates significantly by half to about 16% (49, 53, 57, 68).

The NCCN guidelines recommend pelvic MRI to rule out myoinvasion, lymph node involvement, and ovarian metastasis before continuing fertility-sparing therapy in patients with persistent endometrial cancer after 6 months of unsuccessful hormone therapy (54).

After 9 to 12 months of progesterone therapy, a persistent or progressive disease suggests a tumor that does not respond to hormones anymore, and therefore, treatment should be discontinued. Hysterectomy is the
mainstay of treatment, and further pathological investigation can be performed (36, 51).

The Role of Metformin in Endometrial Cancer

Patients are often encouraged to seek fertility consultation prior to the start of the treatment, as they are often likely to carry a history of infertility, PCOS, or obesity (15, 19). The recognition of the anti-proliferative action of metformin on endometrial cancer cells has led to its use in women with endometrial cancer. The addition of metformin to correct obesity and hyperinsulinemia has been studied as a major risk factor for endometrial cancer and infertility (19). Metformin decreases the Ki-67 proliferation marker, increases PR expression by inhibiting mTOR, sensitizes progesterone-resistant EC cells to apoptosis, and inhibits estradiol-induced proliferation in EC cells by increasing ER-β while decreasing isoform ER-α. Young et al. observed a higher CR rate in EC patients at an oral MA of 160 mg/day + oral metformin 500 mg 3 times daily compared with an oral MA of 160 mg/day alone at 16 weeks of follow-up (34.3% vs. 20.7%, respectively) (69).

Ovarian Preservation

There are 3 main reasons for oophorectomy in endometrial cancer:

1) Ovaries are the main source of estrogen, further supporting the hyperplastic event (23, 24).
2) Possibility of synchronous ovarian malignancies with endometrial cancer (23, 24).
3) Possibility of micro-metastases of endometrial cancer cells to the ovaries (24, 70, 71).

Recent studies suggest that the ovarian metastasis rate is overestimated, and it is around 5% rather than 25% in early-stage EC (23, 24, 72).

Intraoperative extrauterine observation is a highly significant predictor of ovarian involvement (24, 51). Synchronous ovarian involvement is reported in 5% of endometrioid endometrial cancer patients younger than 45 years old, of which only 0.8% had microscopic lesions, which were not grossly visible (23, 72).

However, 2 studies indicated that ovarian involvement was observed in 83.3%-85% of patients through direct observation by the surgeon or preoperative imaging. They suggested a 15% chance of missing a synchronous ovarian involvement (71). In the study conducted by Ashrafganjoei et al., 20 (11.1%) out of 180 endometrial cancer patients had ovarian involvement (73).

Risk factors for ovarian involvement are deep myometrial invasion, high FIGO grade (II/III), lymph node metastasis, and lymphovascular space involvement (LVSI); therefore, careful evaluation in these patients is essential (71).

In conclusion, patient selection criteria for ovarian preservation would involve (23, 33, 54):

1) Age under 45 years old
2) Histology of endometrioid endometrial carcinoma
3) Stage I
4) Low grade
5) Myometrial invasion <50%
6) No ovarian mass either grossly visible or present in the imaging
7) Family history of inherited cancers

Although a large cohort study conducted by the Korean Society of Obstetrics and Gynecology indicates a 4 % recurrence rate in endometrioid endometrial cancer (72), long-term results suggest no difference in disease-free survival and overall survival in the ovarian preserved group (11, 74). Ultimately, a more individualized approach should be taken toward patient selection, and both the patient and physician should be aware of the risks and benefits.

Cryopreservation of Ovarian Tissue

Ovarian tissue cryopreservation with the removal of small antral follicles and freezing immature oocytes have been addressed in the literature, causing both ovarian tissue and isolated immature oocytes to freeze (75). The first successful pregnancy and delivery through this method was described by Prasath et al. (76). The optimum thickness of ovarian tissue to maintain cryopreservation, which can maximize the preservation of primary follicles, is approximately 1 mm (77). Isolation of individual follicles from ovarian tissue and then performing in vitro maturation (IVM) and fertilization might be considered. In another reported method of maintaining fertility, immature oocytes were removed from ovarian tissue and subjected to IVM and vitrification, while ovarian tissue was preserved by cryopreservation (75).

Considering increasing the success rate in maintaining fertility by stimulation of cryopreserved ovarian tissue and also because of a low risk of metastases to ovaries, cryopreservation of ovarian tissue can be applied in early-stage endometrial adenocarcinoma. Fifty percent of the ovaries are resected via laparoscopy, followed by ovarian stimulation 1 to 2 days later. About 2.5 weeks are needed for combination therapy (78).

Oncologic and Fertility Outcomes

Conservative treatment results in complete remission in 76%-82.4% of patients, with a mean of 23% relapse rate (28), but it is important to note that it will not increase the risk of recurrence compared with standard treatment (15). There is a 22% failure rate in conservative treatment, which should be thoroughly discussed with the candidates for fertility preservation.
It is estimated that about 22% will achieve successful pregnancy (79).

Patients successfully achieving 1 pregnancy are reported to have a higher disease-free survival compared to those who did not (19, 36).

Most candidates for fertility preservation have risk factors that are in common with infertility, including polycystic ovarian syndrome, obesity, age, and irregular menses; therefore, they would benefit from assisted reproductive technology (ART) for improved chances of pregnancy (9, 18, 80). In determining fertility outcomes, Wang et al. found no difference in pregnancy and live birth rates between 29 patients with PCOS and 55 non-PCOS patients who reached CR and attempted to conceive. Additional prospective studies are required to assess oncological and fertility outcomes of fertility-sparing treatment in patients with PCOS (81, 82).

**Conclusion**

Oncofertility is not a new concept. It has been addressing the reproductive needs of gynecologic cancers ever since 1959. However, with emerging trends in lifestyle and population characteristics, it seems that the urge for advancement in this field is now more than ever.

Current guidelines and instructions are mainly based on case reports and retrospective studies; moreover, the oncologic results are short-term in many cases and few eligible long-term studies are conducted (36, 49).

Randomized clinical trials are seldom conducted due to ethical issues. Patient gathering and difficulty in following the patients continuously are other obstacles. There is also a possibility for selection bias as younger, healthier patients account for most of the candidates (9, 51). Further prospective trials are required to establish the exact extent of our interventions.

Until then we have concluded that:

1. Simultaneous use of two modalities for tumor suppression yields better outcomes. Complete response rates with oral progestin regimen improved to 80% from 70% when combined with an LNG-IUD. (16, 36, 68) In a similar matter, adding Hysteroscopic resection to oral progestin therapy improved the results to 96.3% and 94.2% regression rates in two separate studies (49, 53).

2. Careful history of hereditary cancers such as Lynch syndrome or HNPCC (Hereditary Non-Polyposis Colorectal Cancer) should be obtained.

3. Salpingo-oophorectomy in young healthy patients can be individualized, carefully balancing the risks and benefits.

4. Although seldom reported, the use of fertility preservation in high-grade tumors is not advised.

5. Pregnancy and reproductive workup should be initiated as soon as possible; as aging, PCOS and other risk factors are often prominent.

Use of Assisted Reproductive Technology is highly recommended, as it improves fertility outcomes dramatically.

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