Fertility preservation in gynecological cancers: an updated overview

Le Viet Nguyen Sa¹, Le Viet Hung¹, Phan Canh Quang Thong¹
¹Center for Assisted Reproduction, Hue Central Hospital
doi: 10.46755/vjog.2024.2.1680
Corresponding author: Le Viet Nguyen Sa, Email: drlevietnguyensa@gmail.com
Received): 5/3/2024 - Accepted: 10/5/2024.

Abstract
Gynecological cancers comprise more than 30% of all cancer mortality in women worldwide and are responsible for an estimated 40% of all cancer incidence. Recently, there has been a significant surge in the prevalence of cancer diagnosis occurring at an earlier stage of life. As the number of cancer survivors increases, the preservation of fertility in women becomes critically important for patients and their families. In light of the fact that surgical excision of the reproductive organs is the primary cause of infertility, the optimal course of action is to modify the surgical approach. We conducted a literature review pertaining to provide a comprehensive summary of the presently accessible treatment approaches for preserving fertility in gynecologic malignancies, along with an analysis of their obstetrical and oncological outcomes.

Keywords: fertility preservation, gynecological cancers, pregnancy, obstetrical, oncofertility.

1. INTRODUCTION
Gynecological cancers, such as breast, cervix, uterine, and ovary cancers, pose a significant public health concern due to their continued contribution to cancer-related deaths. These malignancies comprise more than 30% of all cancer mortality in women worldwide. They are responsible for an estimated 40% of all cancer incidence, with an annual incidence of over 3.6 million cases and mortality exceeding 1.3 million [1]. In addition, recently, there has been a significant surge in the prevalence of cancer diagnosis occurring at an earlier stage of life. From 1990 to 2019, the worldwide incidence of early-onset cancer rose by 79.1%, while the global mortality rate from early-onset cancer increased by 27.7% [2].

Fortunately, the landscape of cancer treatment has been transformed noticeably/tremendously the past two decades, characterized by advancements in early detection techniques, precise cancer-targeting treatments, strategies to minimize radiation exposure, and the development of minimal surgical interventions. Thanks to these breakthroughs, individuals diagnosed with cancer can now live with the disease, which was previously considered fatal, as a manageable condition, ultimately leading to a curable ailment. According to the American Cancer Society, the estimated five-year survival rates for breast cancer, endometrial, cervical and ovarian cancer are 90%, 81%, 66% and 49%, respectively [3]. While modern anticancer therapies have substantially decreased mortality, they have also increased the incidence of undesirable side effects, including infertility. In conjunction with advancing maternal age, an increasing proportion of cancer survivors require fertility preservation in order to achieve family completion [4].

In contrast to other forms of tumors, however, the gonadotoxicity caused by radiation and/or medical treatment did not constitute the primary cause of infertility. Indeed, the anatomical capacity for fertility may be significantly compromised by a gynecologic malignancy diagnosis, to the extent that the surgical procedure induces irreversible damage. The issue of fertility preservation constitutes a significant concern within the given context [5]. Although oncofertility reviews pertaining to women with breast cancer or general cancer have been discussed in the literature, reviews of fertility preservation for young women with gynecologic cancer are scarce. The objective of this literature review was to provide a comprehensive summary of the presently accessible treatment approaches for preserving fertility in gynecologic malignancies, along with an analysis of their obstetrical and oncological outcomes.

2. FERTILITY PRESERVATION TECHNIQUES FOR GYNECOLOGICAL CANCERS
Fertility preservation (FP) strategies are primarily determined by tumor and patient characteristics (stage of disease, histology, treatment, and preference for using sperm from a banked donor or a companion). Moreover, the provision of oncofertility counseling is an essential measure in educating cancer patients about the potential for treatment-induced premature ovarian failure and infertility associated with the anticancer therapies under consideration. Additionally, this counseling should outline the various viable alternatives for conserving ovarian function and fertility, weighing the advantages and disadvantages of each. Fertility preservation techniques pertaining to each gynecological malignancy are provided in Figure 1 [5].
2.1. Cervical cancer

Uterine cervical cancer (UCC) is the fourth most common malignancy in women worldwide. Although survival rates have increased as a result of social screening and treatment protocols for UCC, the surgical, radiological, and chemotherapy-based therapeutic approach to this disease may significantly impair female fertility and have a negative impact on ovarian function, leading to premature menopause and early ovarian insufficiency. Consequently, FP in women with UCC constitutes a developing and intriguing topic. Age at diagnosis, parity, desire to become pregnant, ovarian reserve status, and time available between cancer diagnosis and treatment initiation, in addition to tumor stage, malignancy grading, and prognosis, must be evaluated in relation to the therapeutic approach to the disease [6].

Cervical cancer is the most prevalent and prime candidate for fertility-sparing surgery in its early stages, owing to its epidemiological characteristics. In contrast, other FP approaches are advised for the advanced and metastatic stages. Several FP strategies are presently accessible in UCC, as detailed in Table 1.

### Table 1. Staging of cervical cancer, treatment and related fertility preservation approach [6]

<table>
<thead>
<tr>
<th>UCC stage</th>
<th>Treatment</th>
<th>Fertility preservation approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA1</td>
<td>Conization</td>
<td>Conization</td>
</tr>
<tr>
<td>IA2, IB, IIA</td>
<td>Combined radiation with brachytherapy and radical hysterectomy with lymphadenectomy Cisplatin-based chemotherapy with radiation (if high-risk features such as positive lymph nodes, surgical margins and/or parametria)</td>
<td>Fertility-sparing surgery (Radical vaginal trachelectomy with pelvic lymph node dissection)</td>
</tr>
</tbody>
</table>
### Advanced disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIB, III, IVA</td>
<td>Cisplatin-based chemotherapy with radiation</td>
</tr>
<tr>
<td></td>
<td>Ovarian suppression with GnRHa before/during CHT</td>
</tr>
<tr>
<td></td>
<td>Ovarian transposition before RT Oocyte cryopreservation before neo-adjuvant CHT or combined CHT-RT Ovarian cortex cryopreservation In vitro differentiation of OSCs</td>
</tr>
</tbody>
</table>

### Metastatic disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVB, recurrent cancer</td>
<td>Cisplatin as palliative, radiation therapy for control of bleeding and pain and systemic chemotherapy for disseminated disease</td>
</tr>
<tr>
<td></td>
<td>Although it is ethically inadvisable, it is nonetheless applicable a gestational surrogacy</td>
</tr>
</tbody>
</table>

#### 2.1.1. Fertility sparing surgery

A distinct strategy is determined for each disease stage. In early stages of cervical cancer (IA-IB1), conization and trachelectomy are typically performed; whereas, for advanced stages (IB1), the current standard recommendation is radical therapy (RT) with or without chemotherapy (CHT), although neoadjuvant CHT followed by radical surgery is a viable alternative. In addition, conization alone, in the absence of lymphovascular space invasion (LVSI) for stage IA1 disease, is a safe alternative to lymphadenectomy, given its exceedingly low incidence of lymphatic metastasis (less than 1%). Fertility preservation is achieved most effectively through radical trachelectomy in conjunction with laparoscopic pelvic lymphadenectomy in the case of LVSI [5-7].

According to the European Society of Gynaecological Oncology (ESGO) guidelines, the criteria for fertility sparing surgery include being of reproductive age, having a desire to preserve fertility, having tumors up to 2 cm in diameter, and having specific histological types such as squamous cell/adenosquamous carcinoma and adenocarcinoma. Additionally, there should be no parametrial invasion, lymph node metastases, or known infertility. Neuroendocrine and non-HPV-associated adenocarcinoma are not suitable for conservative treatment [8], [9].

In addition, neoadjuvant chemotherapy followed by conization or simple/radical trachelectomy may serve as a viable FP strategy for tumors measuring 2 to 4 cm in diameter (IB2), yielding comparable results to conventional management (8.5% recurrence rate). Constraints should be placed on the availability of conservative surgical treatment for patients with the IB2 stage, as it is still regarded as an experimental method [6], [7].

#### 2.1.2. Oncology results

In terms of oncological safety, conservative surgery performed in accordance with indication criteria is identical to radical hysterectomy. Recurrence and 5-year mortality rates are 3.6-6% and 1.6-5%, respectively, for radical trachelectomy [8]. Zhang et al [10] conducted a review and meta-analysis which revealed that the recurrence rates for stage FIGO 2008 IA and IB tumors undergoing conization were 0.4% and 0.6%, respectively, in 2854 patients. The results of the various fertility-sparing procedures (conization, vaginal radical trachelectomy, abdominal trachelectomy, and mini-invasive trachelectomy) were compiled in 53 studies according to a more recent review. Conization, vaginal radical trachelectomy, abdominal trachelectomy, and mini-invasive trachelectomy each had a recurrence rate of 4.2%, 4%, 3.9%, and 4.2%, respectively [11]. Recurrence rates were correlated with LVSI and tumor size exceeding 2 cm.

#### 2.1.3. Obstetrical outcomes

Infertility following radical trachelectomy affects 14-41% of patients, with some individuals needing assisted reproductive methods [12]. First-trimester abortion rates are similar to those of the general population, although second-trimester miscarriages occur more frequently. 28-38% of pregnant women experience premature/preterm birth, with 12% occurring before 32 weeks [13].

Zhang’s literature review and meta-analyses [10] suggest that conization results in reduced recurrence rates and improved oncological outcomes. The incidences of pregnancy, miscarriage, and premature delivery were 36.1%, 14.8%, and 6.8% respectively, compared to 20.5%, 24%, and 26.6% in cases of trachelectomy. The pregnancy rate following vaginal, abdominal, and laparoscopic radical trachelectomies was 37.8%, 10.4%, and 9.2%, respectively, in a recent review by Smith et al. [14]. The corresponding live-birth rates were 75.7%, 75.6%, and 57.1%. Preterm birth occurred in 33.9%, 39%, and 57.1% of cases, following radical trachelectomies performed vaginally, abdominally, and laparoscopically respectively.

Pregnancy is classified as high risk due to an increased risk of complications including premature rupture of membranes and preterm delivery. Therefore, antenatal care should be administered at a referral center. There is insufficient evidence from observational studies supporting the recommendation of particular procedures for these patients. Ultrasound-guided
cervical length monitoring, vaginal progesterone and vaginal cerclage, as well as detection of asymptomatic bacteriuria are all suggested. Priority is given to elective cesarean section [9].

2.1.4. Follow up

Reviews every 3 - 4 months for the first two years, six months for the third to fifth years, and annually after that. Annual cervicovaginal cytology is advised. The recommended follow-up term for pregnancy is 6-12 months. After pregnancy, radical treatment is not recommended [8], [9].

2.2. Endometrial cancer

Endometrial carcinoma (EC) is the sixth most frequently diagnosed malignancy among women globally, and its prevalence is on the rise among those who have completed menopause [15]. Despite having a median age of 63 years at diagnosis, 7% of patients are diagnosed with EC before the age of 45. EC is typically managed surgically through hysterectomy, bilateral salpingo-oophorectomy, and staging [16]. Early-stage, low-grade disease in younger patients has been associated with enhanced survival, according to an analysis of the SEER database [17].

2.2.1. Conservative treatment

Selection criteria

According to the current National Comprehensive Cancer Network (NCCN) [18]/ European Society of the Gynecological Oncology Task Force Recommendations for Fertility preservation [19]:

1. Well-differentiated (grade 1) endometrioid cancer on D&C confirmed by expert pathology.
2. MRI (preferred) or transvaginal ultrasound showing endometrial disease.3. No suspected or metastatic illness on imaging.
4. No medical or pregnancy contraindications.
5. Patients should be informed that fertility-sparing endometrial cancer treatment is not standard.

Guidelines from the Royal College of Obstetricians and Gynecologists and the British Gynecological Cancer Society expand the selection criteria to include women who have superficial myometrial invasion [20].

Although the majority of EC is caused by sporadic mutations, mutations associated with Lynch syndrome account for approximately 5 - 9%. Genetic counseling and germline testing are advised for patients with a significant familial predisposition to colorectal and/or colon cancer. This is particularly crucial for women under the age of 50 who have been diagnosed with cancer, as Lynch syndrome is linked to an elevated risk of developing secondary malignancies, including ovarian or colorectal cancer [16].

Fertility Preservation Options

Hormonal Treatment Modalities

Hormonal therapy, including intrauterine levonorgestrel devices (LNG-IUD) or oral systemic progestogens (e.g., medroxyprogesterone acetate (MPA) or megestrol acetate (MA), is the preferred conservative approach. Doses of medroxyprogesterone acetate vary from 2.5 to 1,500 mg per day, with 400-600 mg being the most common. Daily quantities of MA reported range from 10 to 400 mg, with the most prevalent range being 160-320 mg. There is a lack of agreement on the best dosage or selection of medication, and the reported dose and treatment duration differ significantly among research. Some studies indicate that lower doses, such as 10 mg/day of MPA and 160 mg/day of MA, may induce improved responses. The duration of treatment can range between eight weeks and nine months [9], [16], [21]. Possible adverse effects include weight gain, thrombosis, mood fluctuations, headache, and tension in the breasts [9].

Levonorgestrel IUD (LNG IUD) systems release constant doses of progestins to the endometrium with limited systemic absorption and few side effects; they are increasingly used for the fertility-preserving treatment of EC [16]. The LNG-IUD can be administered alone or in combination with systemic progestogen, with the combination being the preferable option [9]. Alternative medications, including aromatase inhibitors, GnRH analogs, and metformin, are also suggested [9].

Surgical Treatment Modalities

Hysteroscopic resection followed by progestins releasing through an intrauterine device (IUD) or oral route has been widely acknowledged as an effective strategy for patients with early-stage EC who desire to continue having children [9], [16], [21]. The findings of a recent meta-analysis indicate that the complete response rate was greatest among patients who underwent progestin therapy after hysteroscopic resection [22].

In contrast to hysterectomy, conservative treatment carries a higher risk of recurrence or persistent disease; therefore, surgical staging becomes necessary following pregnancy. Women under the age of 45 have a 4 - 25% likelihood of developing synchronous ovarian cancer, even at a presumed early stage. The potential involvement of LS in the etiology of the tumor in a young patient whose molecular diagnosis presents challenges for conservative therapy constitutes an additional cause for concern. Preserving exclusively the ovaries which appear macroscopically normal is an alternative approach to conservative surgery [9].

2.2.2. Oncology results

Complete response rates vary between 48% and 96% when all treatment modalities are considered. The recurrence rate for patients who attain a complete response varies between 25% and 47%. In 63 - 96% of patients, treatment with LNG-IUD with or without oral progestin results in a complete response [9]. A recent meta-analysis revealed that 35.3% of cases recurred, while 79.7% achieved complete response [9], [23]. After
six months, the complete response rates for patients with G1 adenocarcinoma and atypical hyperplasia who were randomized to receive LNG-IUD treatment alone as opposed to the combination of weight loss and metformin use were 61%, 67%, and 57%, respectively. Considering adenocarcinoma and atypical hyperplasia in the three groups, remission occurred in 43% and 82%, respectively [9], [24].

2.2.3. Obstetric results
The literature reports that the pregnancy rate for hormonal treatment alone ranges from 35 to 60%. However, when hysteroscopic and hormonal treatments are combined, the pregnancy rate increases to approximately 70%. In the 4 to 66 months following conservative treatment, the recurrence rate for EC is 30-40%, progestin re-treatment is an option [25]. Pregnancy is recommended as soon as neoplasm remission is achieved (two negative biopsies), since there is a risk of recurrence [9], [26].

2.2.4. Follow-up
The patient is alerted about bleeding and given lifestyle advice. Endometrial sampling by dilation and curettage or hysteroscopic biopsy is performed every 3 - 6 months. Two consecutive complete response endometrial biopsies with a minimal interval of 3 months are necessary to consider the success of the fertility-sparing treatment and to recommend pregnancy. If there is no response, increase the progestin dose and follow the quarterly control. If there is no response or progression after nine months, definitive surgical treatment is indicated [9], [18], [23], [26].

2.3. Ovarian cancers
The mortality rate associated with ovarian cancer ranks second among all gynecological malignancies. A majority of patients, exceeding two-thirds, receive a diagnosis at an advanced stage. 11.8% manifest prior to the age of 45, typically in the early stages and with a more favorable prognosis, while the majority transpire subsequent to menopause. The diagnosis of ovarian cancer in young women gives rise to apprehensions regarding their fertility [9], [27].

2.3.1. Managing a desired pregnancy woman
Fertility sparing surgery can be suggested depending on the histology, stage of disease and preexisting ovarian reserve, but there is not a consensus on the criteria for conservative approach. Therefore, until appropriate staging has been achieved, conservative surgery should be considered, and it should be strictly followed up on [28]. In addition, the patient should be aware that intraoperative frozen section has limits, with sensitivity and specificity of approximately 90% and 99.5%, respectively. When a frozen section diagnosis indicates a borderline tumor, 21% of instances will later reveal an invasive tumor in the paraffin results. The fertility-preserving surgical strategy may thus be modified in light of the conclusive histopathological outcome. Many publications recommend a two-step management approach for suspected ovarian lesions in patients who want to preserve fertility, waiting for the conclusive histology results before making a choice. Fertility-sparing surgery allows for the preservation of the uterus with or without preserving the contralateral annex [9].

On the basis of their origins, ovarian malignancies are typically divided into two categories: epithelial ovarian cancers (EOCs) and non-EOCs, which include germ cell tumors, sex–cord–gonadal stromal tumors, and borderline tumors. Patients who have juvenile granulosa cell tumors and germ cell tumors, as well as those who have early-stage EOC and borderline ovarian tumors, may qualify for fertility preservation. The information gathered on fertility-sparing surgery in ovarian tumors was sump up in Table 2 [28].

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Fertility sparing surgery</th>
<th>Indications and limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borderline tumors</td>
<td>Unilateral salpingo-oophorectomy or cystectomy</td>
<td>- Limited disease</td>
</tr>
<tr>
<td></td>
<td>+ Complete surgical staging:</td>
<td>- Unilateral salpingo-oophorectomy is preferred – lower risk of recurrence (8%);</td>
</tr>
<tr>
<td></td>
<td>- Abdominal cavity exploration;</td>
<td>- Second salvage surgery may be necessary - possible recurrent borderline lesions on the contralateral ovary;</td>
</tr>
<tr>
<td></td>
<td>- Peritoneal washings;</td>
<td>- Minor foci of typical endometrioid adenocarcinoma at pathological examination is possible.</td>
</tr>
<tr>
<td></td>
<td>- Infracolic omentectomy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Multiple peritoneal biopsies.</td>
<td></td>
</tr>
</tbody>
</table>
Patients with ovarian tumors suspected of carrying malignancy are advised to undergo oocyte or embryo cryopreservation, given that the definitive histologic diagnosis may alter the therapeutic approach.

### 2.3.2. Oncology results
Fertility-sparing surgery for early-stage ovarian cancer is linked to relapse rates of 9% - 29%, 5-year survival rates of 83% - 100%, and a 5% recurrence rate in the remaining ovary [28].

### 2.3.3. Obstetrical results
A recent study found no adverse obstetric outcome in pregnancies following fertility-sparing surgery for ovarian cancer in comparison to low-risk pregnancies [29]. A systematic review of 120 studies revealed that 54% of patients treated conservatively for ambiguous tumors achieved pregnancy [30]. More recently, Yu-Fei Zhang’s meta-analysis found that fertility-sparing surgery in stage I epithelial ovarian cancer patients yields promising reproductive outcomes, with a high rate of ovarian function preservation and successful pregnancies. Pooled pregnancy was 30% (95% CI: 0.26 - 0.34), whereas pooled natural conception comprised 26% (95% CI: 0.20 - 0.33) [31].

### 3. ASSISTED REPRODUCTIVE OPTIONS
Assisted reproductive technologies (ART), including controlled ovarian hyperstimulation (COH) cycles and oocyte and embryo cryopreservation, may efficiently preserve fertility in the face of threatening ovarian reserve exhaustion resulting from planned gonadotoxic chemotherapy/radiotherapy or surgical ovary removal. However, the increased circulating estradiol levels caused by the simultaneous formation of numerous large follicles, which can worsen the prognosis for estrogen-sensitive cancers, are a significant concern with conventional COH protocols [32]. Existing strategies aim at maintaining low estrogen levels during controlled ovarian hyperstimulation (COH), thereby ensuring the safety of patients with estrogen-dependent cancer and preventing an increased risk of cancer recurrence. Ovarian stimulation combined with letrozole 2.5 – 5 mg daily is suggested by the fertility preservation network FertiPROTEKT for patients with estrogen-sensitive malignancies, including granulosa cell tumors, endometrial cancer and breast cancer. In addition, tamoxifen was incorporated into these protocols in an effort to reduce the estradiol peak [33]. Also, for fertility preservation, the “random-start protocol” involves administering gonadotropin any day of the menstrual cycle, late follicular, peri-ovulatory, or luteal phase. The “random-start protocol” takes 2 weeks instead of 4 - 5 weeks to complete fertility preservation, and it can be used for any patient, even those with IUDs. Two egg retrievals in 28 days are followed by a second ovarian stimulation cycle four days after the first egg collection in the “duo-stim” approach [34].
Cryopreservation of embryos and oocytes is the most well-established method for preserving fertility when the patient does not require cancer treatment immediately [5]. The primary distinction between these methods is that the oocyte is the property of the patient and not the couple [9]. When a COH cycle is not feasible, patients may undergo ovarian tissue cryopreservation (OTC) and subsequent autotransplantation (OvTx) instead of embryo and oocyte cryopreservation (ART). OTC preserves several follicles in the ovarian cortex and can be done at any time throughout menstruation. After oncological treatment, frozen-thawed ovarian cortical tissues can be implanted [32]. Reimplantation of concealed tumor cells within the cryopreserved ovarian tissue is a concern associated with this procedure. Nevertheless, no indication of cancer cells in cryopreserved ovarian tissues was detected in ovarian samples obtained from patients with nonmetastatic breast, bone, and soft tissue malignancies. Thus, the risk of cancer cell reintroduction following OvTx appears extremely improbable in early-stage endometrial and cervical malignancies devoid of ovarian involvement. In all circumstances, however, it is advised that frozen-thawed ovarian samples be histologically examined for malignant cells prior to transplantation [32].

In certain patients who have been diagnosed with EC, a hysterectomy is strongly recommended. Parenthood can still be achieved with the assistance of a gestational surrogate and cryopreserved oocytes or embryos in these circumstances [16]. In Vietnam, surrogacy for humanitarian purposes has been allowed in Vietnam from 2015 and gestational carriers are identified directly by patients when family members are volunteering for the service.

4. CONCLUSIONS

Preserving reproductive capacity in women with gynecologic cancer is possible without affecting survival, while facing several challenges. Therefore, a personalized multidisciplinary strategy and prompt referral to a reproductive specialist are essential for optimal outcomes for women seeking to preserve their fertility. Fertility-preserving treatment for women with gynecological cancer is based on the patient’s wish and ability to conceive, while ensuring that it does not negatively impact the cancer treatment’s effectiveness. Careful selection is a crucial element of this process. Patients eligible for conservative treatment should get comprehensive care from a multidisciplinary team at a specialized center, including reproductive counseling from an assisted reproduction expert. Assisted reproductive procedures do not affect the outcome and can enhance reproductive outcomes alongside traditional surgical treatment.

REFERENCES