

REVIEW ARTICLE

Fertility preservation in gynecological cancers

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Summary

Fertility preservation has become a component of cancer survivorship care as increasing numbers of young women with malignancies seek to retain reproductive potential. This review summarizes fertility-sparing approaches in gynecologic oncology, emphasizing individualized patient selection, multidisciplinary collaboration, and timely referral to reproductive specialists.

Fertility-sparing treatment for endometrial, cervical, and ovarian cancers may be applied in carefully selected patients. In endometrial cancer, conservative management is done by hysteroscopic resection followed by progestin therapy. After complete response, pregnancy may be pursued, and assisted reproductive technology can be considered, particularly in patients with advanced age or previous infertility.

In cervical cancer, fertility-sparing treatment primarily involves conization or trachelectomy in selected early-stage tumors. Tumor size, stromal invasion, lymph node status, metastatic disease, involvement of the internal cervical os, and surgical margins are key determinants of eligibility. Trachelectomy allows preservation of the uterus, although pregnancy rates are lower than in the general population and obstetric complications, particularly pregnancy loss and preterm birth, remain relevant.

For ovarian cancer, fertility-sparing surgery consists of unilateral salpingo-oophorectomy with comprehensive staging while preserving the uterus and contralateral ovary. It is appropriate for selected early-stage epithelial tumors and non-epithelial malignancies, while borderline tumors may be treated conservatively at all stages. Fertility outcomes are favorable, although ovarian reserve may be reduced by surgery and chemotherapy.

Overall, fertility-sparing treatment is feasible for appropriately selected patients with gynecologic malignancies. Outcomes require individualized oncologic assessment, close surveillance, and coordinated oncofertility care.

Keywords: oncofertility, fertility-sparing surgery, gynecologic oncology, pregnancy after cancer treatment

INTRODUCTION

According to world statistics, cancer incidence rises in women more than in men and presents a growing clinical and public health challenge (1). Because of increasing maternal age and changes in human fertility, as well as better survival rates, we are facing more and more young, reproductively active patients with malignancies who wish to preserve fertility. Still, we must postpone family planning because of cancer (2). Therefore, diagnosis and treatment have improved substantially over the past few decades, improving survival rates and quality of life (3). In 2025, the American Society of Clinical Oncology updated its clinical practice guideline on fertility preservation in patients with cancer and stated that fertility sparing is included in survivorship care (4). Fertility preservation options offer patients hope by showing that survival and fertility are not mutually exclusive. Studies show that three-quarters of cancer survivors would like to achieve pregnancy after treatment (5). A multidisciplinary team is involved; close collaboration and coordination between oncologists and reproductive endocrinologists are especially important.

Surgical procedures, a cornerstone of gynecological oncology, may disrupt the hormonal axis, diminish reproductive function, and directly affect oocytes (6). Adjuvant anticancer treatments, especially alkylating chemotherapy and pelvic radiotherapy, are often gonadotoxic and may disrupt endocrine function, causing premature ovarian insufficiency, infertility, early menopause, and associated psychosocial distress (7). Therefore, pretreatment assessment of treatment-related gonadotoxicity and risk estimation is essential. All patients who are candidates for fertility-sparing treatment must be informed in advance about the potential impact of cancer treatment on fertility and should be referred to reproductive specialists as early as possible (8). The risk is estimated based on patient-related, disease-related, and treatment-related factors (9). The single most important factor is the patient's age (9). Oncofertility as a multidisciplinary, emergency, and time-sensitive field helps people to save fertility while fighting against cancer (10).

Fertility-sparing surgery in gynecologic oncology is an important part of oncofertility practice that has proven safe in carefully selected cases according to the recommendations of professional societies. The feasibility of fertility-sparing treatments in early-stage ovarian, endometrial, and cervical cancer is not only dependent on timely diagnosis and better screening programs, but also on advances in imaging techniques, better understanding of tumor biology, and availability of effective adjuvant therapy. Each patient needs a careful, individualized approach (considering tumor type, stage, histology, grade, molecular characteristics, age, ovarian reserve, treatment urgency, and reproductive wishes) to avoid a one-size-fits-all approach (11).

The Clinic for Gynecology and Obstetrics, University Clinical Center of Serbia, is a national center for fertility preservation and oncofertility, offering both fertility-sparing surgery and a cryopreservation program.

FERTILITY PRESERVATION IN ENDOMETRIAL CANCER

The sixth most common cancer worldwide in females is endometrial cancer (12). The most common pathological type is endometrioid endometrial cancer, which is hormone-dependent. Almost 80% are diagnosed in the initial stage and have an excellent survival rate of more than 95% (13). Although it mostly affects postmenopausal women, the incidence is rising in women under the age of 45. Four percent are even younger than 40 (13). Risk factors for endometrial cancer are well established, mostly modifiable, and represent an important part of the treatment. The overlap between infertility, metabolic dysfunction, and malignancy is particularly evident in endometrial cancer. Standard surgical treatment of endometrial cancer and endometrial intraepithelial neoplasia is hysterectomy with or without bilateral salpingo-oophorectomy. Because of its hormonal dependence and high survival rate, conservative hormonal treatment may be considered under certain conditions. In 2023, as a result of collaboration among three esteemed gynecological societies (European Society of Gynecological Oncology – ESGO, European Society for Human Reproduction and Embryology – ESHRE, and European Society for Gynecological Endoscopy – ESGE), a fertility-sparing guideline for endometrial carcinoma was issued for the first time (14). Certain criteria must be met to start conservative treatment. Firstly, it is important to have a second opinion from an expert pathologist since the distinction between endometrial cancer and hyperplasia is sometimes challenging, and there is poor intra- and inter-observer agreement (15). Fertility-sparing treatment may be applied in cases of endometrioid pathology, Grade 1, Stage IA, and without myometrial invasion (14). Hysteroscopy with endometrial biopsy is the gold standard for endometrial evaluation, and it should be performed both for diagnosis and for follow-up (14).

Evaluation of the myometrium and possible extrauterine disease is a very important step, for which pelvic MR or expert transvaginal ultrasound is done. Systematic review and meta-analysis showed similar performance for both techniques (16). Nowadays, the established protocol for fertility preservation for endometrial cancer is hysteroscopic resection followed by progestin therapy. Progestin-based therapies include oral progestin (megestrol acetate at a dose of 160–320 mg/day or medroxyprogesterone acetate at a dose of 400–600 mg/day) or an intrauterine device with levonorgestrel for 6 months (14). Although GnRH analogs are a second-line treatment

according to the 2023 Guideline, many studies have shown comparable results (17). Treatment duration can be extended to 12 months but not beyond 15 months. After treatment, hysteroscopy is done. If there is a complete response on two consecutive pathological findings with an interval of at least 3 months, pregnancy is advised (14). According to current studies, there is no contraindication for assisted reproductive technology (ART) to achieve pregnancy (18). Furthermore, these patients are often over 35 years of age and have a previous history of infertility treatment and insulin resistance, so timely referral to ART after completion of oncological treatment is recommended (19, 20). Studies show that a combination of hysteroscopic resection and progestin treatment shows promising results, with pregnancy rates as high as 93%, although not all patients try to conceive (17).

However, several areas of uncertainty remain, including Grade 2 tumors, tumors with minimal myometrial invasion, and patients with Lynch syndrome. Molecular classification is now integrated into endometrial cancer staging and provides valuable information for treatment choice, but larger studies are needed to estimate its clinical usefulness (21, 22).

FERTILITY PRESERVATION IN CERVICAL CANCER

Although the incidence of cervical cancer is decreasing in developed countries, around 20% is still diagnosed in young women who have not completed reproduction (23). Abdominal and vaginal radical trachelectomy remain important fertility-sparing options for selected patients, although the choice of surgical approach should be individualized according to tumor size, histological type, lymphovascular invasion, nodal status and preference and skills of the surgeon. In carefully selected cases in patients with a strong desire to preserve fertility, trachelectomy is performed. Selection criteria are based on clinical examination and imaging, while favorable histological types are confirmed by cervical biopsy or conization (24). Histological types include all-grade squamous cell carcinoma or all grades of usual-type HPV-associated adenocarcinoma. Studies have shown that MRI outperforms CT and clinical exam in defining tumor size and surrounding structures, including internal os involvement and vaginal, bladder, and rectal invasion (25). Also, MRI proved best for nodal involvement (25). Oncological selection criteria that must be met are as follows: tumor size of less than 2 cm, stromal invasion less than 10 mm, negative pelvic lymph node status, no evidence of any metastasis, no internal cervical orifice tumor involvement, and the distance from the internal orifice to cervical tumor is more than 10 mm on imaging (26). Finally, free margins on final pathology must be obtained (26). According to guidelines for the management of patients with cervical cancer, conization and

simple trachelectomy are possible in patients with FIGO IA1 and IA2 stages, regardless of LVSI invasion, as well as for IB1 stage, with LVSI-negative tumors (27). Radical trachelectomy is performed in patients with IB1 and LVSI positive tumors (27). Nowadays, there has been a shift towards a less radical approach given the favorable prognosis and high survival rates for early-stage cervical cancer (23). This reflects the growing importance of reducing long-term morbidity and improving quality of life without compromising oncological safety. The debate is also on whether to preserve the uterine artery (28). FIGO cervical cancer staging 2018 update introduced a distinct stage IB2 when the tumor size is 2-4 cm (29). Although patients staged IB2 are at higher risk of recurrence, fertility-sparing treatment may be considered after in-depth discussion. Neoadjuvant chemotherapy (NACT) is a proposed option in these cases, followed by abdominal radical trachelectomy, which has shown the lowest recurrence rate (26). However, this approach remains under investigation, and its oncological safety and reproductive outcomes require further evaluation (26). Negative pelvic lymph node status should be obtained before NACT (27). Sentinel lymph node (SLN) mapping plays an important role in the surgical management of early-stage cervical cancer. SLN assessment may guide the extent of lymph node surgery, support individualized treatment decisions, and reduce morbidity (27).

The goal of fertility preservation is an uneventful pregnancy, so an important consideration is cerclage following trachelectomy. Some uncertainties remain regarding cerclage, including the optimal technique and timing of cerclage placement (30). According to the literature, pregnancy rate after trachelectomy is lower than in the general population, but a higher live birth rate was achieved in patients with uterine artery preservation (31). Interestingly, patients after abdominal trachelectomy attempt less to conceive than patients after vaginal and endoscopic trachelectomy (31). Although pregnancy rates vary, complication rates are similar among studies and include first-trimester and second-trimester pregnancy loss and preterm birth (30). Close follow-up after treatment with HPV testing and cytology is important.

FERTILITY PRESERVATION IN OVARIAN CANCER

Ovarian neoplasms are heterogeneous, with varying malignant potential and aggressiveness, including both epithelial and non-epithelial tumors. Unlike endometrial cancer, epithelial ovarian cancers are often diagnosed in advanced stages and have poorer prognosis (32). On the other hand, non-epithelial ovarian cancers are mostly found in younger women who have not yet completed reproduction (33). This subgroup comprises predominantly unilateral and histologically diverse tumors, diagnosed in early stages and with a high survival rate, so

conservative surgical treatment is the standard of care for women of reproductive age (6).

Fertility-sparing treatment for ovarian cancers has become an established option in carefully selected patients with a strong desire to preserve fertility. It implies unilateral salpingo-oophorectomy and surgical staging, including peritoneal washings, omentectomy, peritoneal biopsies, and lymphadenectomy. This enables future pregnancy by preserving the uterus and contralateral ovary.

This kind of treatment is reserved only for stage IA and IC1 epithelial ovarian cancers. More specifically, ovarian preservation is acceptable for low-grade serous and low-grade endometrioid tumors stage IA and IC1, high-grade serous IA, mucinous tumors with expansile invasion IA and IC1, mucinous with infiltrative invasion IA and clear-cell stage IA and IC1 (26). Complete surgical staging is especially important for epithelial ovarian cancers because 30% of patients have a higher stage of disease than upon initial imaging evaluation (32). Adequate surgical staging is mandatory before proceeding to cryopreservation techniques. Fertility-sparing treatment is selected for non-epithelial ovarian tumors in cases of germ cell tumors - all stages, granulosa cell tumors stage IA and IC1, and Sertoli-Leydig cell tumors IA (26). Malignant ovarian germ cell tumors are platinum-chemo-sensitive tumors, so if cryopreservation is desired, it is ideally performed before chemotherapy. Ovarian stimulation and pregnancy should be postponed at least 6 months after the last chemotherapy to minimize its teratogenic effect (32). Some studies suggest delaying pregnancy for 2 years after completion of cancer treatment to allow for adequate oncological follow-up and reduce the risk of recurrence, while also reducing the potential impact of treatment on pregnancy and fetal outcomes (34).

A distinct subgroup of ovarian neoplasms is borderline tumors with excellent prognosis, even in advanced stages (26). So, fertility-sparing surgery is applied in all stages, and it has not shown worse outcomes when compared to radical treatment (35). Even cystectomy (unilateral or bilateral) may be considered for serous or seromucinous histological types, but patients must be aware that the recurrence rate is 30% (36).

Studies have shown that the conception rate after fertility-sparing treatment ranges from 60-100%, and the risk for both mother and baby was not increased when conception occurred at least 3 months after surgery (32, 37). Assisted reproductive technology following fertility-sparing treatment for ovarian neoplasms presents unique challenges, including diminished ovarian reserve from prior surgery and chemotherapy, concerns about hormonal stimulation and the need for timing of conception relative to surveillance intervals and recurrence risk (26, 38).

FERTILITY PRESERVATION PROGRAM FOR ONCOLOGICAL PATIENTS

The cryopreservation method depends on tumor type and stage, treatment type, individual characteristics, age, and ovarian reserve. The counseling should be offered to every patient, ideally before gonadotoxic treatment (3). The greatest obstacle is time, and sometimes fertility preservation after treatment is indicated. The most prevalent malignancies among young females who seek fertility preservation are breast cancer, hematological malignancies, thyroid cancer, and gynecological cancer, and for males, testicular cancer and hematological malignancies (3). Cryopreservation techniques in women include oocyte cryopreservation, embryo cryopreservation, ovarian tissue cryopreservation, pharmacological ovarian suppression with a GnRH agonist, ovarian transplantation, and shielding. Embryo and oocyte cryopreservation are the treatment of choice for reproductive-age women when ovarian stimulation can be performed (4). Random-start protocols are well established and shorten the delay to cancer treatment. Ovarian tissue cryopreservation is reserved for prepubertal girls and in urgent cases when treatment cannot be postponed. Fertility preservation techniques in males are sperm cryopreservation and testicular tissue preservation. Hormone-sensitive tumors, such as breast cancer, raise concern about the safety of stimulation. Letrozole is safe for these patients (39). Another issue is possibility of reintroducing malignant cells in hematological malignancies after ovarian reimplantation (3). Therefore, fertility preservation decisions should be made by a specialized team, with attention to the cancer prognosis, general condition of the patients, storage duration, costs, and legal framework (3).

CONCLUSION

Overall, fertility-sparing treatment is feasible for appropriately selected patients with gynecologic malignancies. Fertility preservation should be offered in all oncological patients. Outcomes require individualized oncologic assessment, close surveillance, and coordinated oncofertility care.

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OČUVANJE FERTILITETA KOD GINEKOLOŠKIH MALIGNITETA

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Sažetak

Očuvanje plodnosti postalo je sastavni deo brige o pacijentima kod kojih je dijagnostikovana maligna bolest, s obzirom na to da sve veći broj mladih žena sa malignitetima želi da sačuva reproduktivni potencijal.

Konzervativno lečenje karcinoma endometrija, karcinoma grlića materice i karcinoma jajnika može se primeniti kod pažljivo odabranih pacijentkinja u ranim stadijumima bolesti. Kod karcinoma endometrija, konzervativni tretman podrazumeva histeroskopsku resekciju praćenu terapijom progestinima. Nakon postizanja potpunog odgovora na terapiju, može se planirati trudnoća i razmotriti primena metoda potpomognute reprodukcije, naročito kod pacijentkinja starije životne dobi ili onih sa prethodno dijagnostikovanim neplodnošću.

Kada je reč o karcinomu grlića materice, lečenje uz očuvanje plodnosti prvenstveno obuhvata konizaciju ili trahelektomiju. Veličina tumora, invazija strome, status limfnih čvorova, prisustvo metastaza, zahvaćenost unutrašnjeg materičnog ušća i hirurške margine predsta-

vljaju ključne faktore za procenu podobnosti za ovaj vid lečenja. Trahelektomija omogućava očuvanje materice, iako su stope začeća niže u odnosu na opštu populaciju, a rizik od akušerskih komplikacija – posebno gubitka trudnoće i prevremenog porođaja – ostaje značajan.

Kod karcinoma jajnika, hirurški zahvat kojim se čuva plodnost sastoji se od unilateralne adneksotomije uz hirurško stadiranje bolesti. Ovaj pristup je pogodan za određene rane stadijume epitelijskih i neepitelijskih tumora, dok se *borderline* tumori mogu lečiti konzervativno u svim stadijumima bolesti. Ishodi u pogledu plodnosti su povoljni, iako hirurška intervencija i hemioterapija mogu dovesti do smanjenja rezerve jajnika.

Lečenje uz očuvanje plodnosti je izvodljivo kod odgovarajuće odabranih pacijentkinja sa ginekološkim malignitetima. Ishodi zahtevaju individualizovanu onkološku procenu, pažljivo praćenje i koordinisan pristup u oblasti onkofertiliteta.

Ključne reči: onkofertilitet, poštedni hirurški tretman, ginekološka onkologija, trudnoća nakon lečenja karcinoma

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