Fertility preservation in women with early-stage gynecologic cancer: optimizing oncologic and reproductive outcomes

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ABSTRACT

Almost all standard therapies for gynecologic cancer, including surgical intervention, gonadotoxic chemotherapy, and radiation therapy, threaten a woman’s childbearing potential. Preservation of fertility should be discussed with premenopausal women with early-stage gynecologic cancer shortly after diagnosis and, for women who desire to preserve fertility, during treatment planning. Many authors have investigated both oncologic and reproductive outcomes following fertility-sparing therapy, and there is ongoing development of assisted reproduction techniques available to cancer patients and survivors. Women with early-stage (IA1-IB1) cervical cancer may be candidates for fertility-sparing cervical conization, simple trachelectomy, or radical trachelectomy. In women with stage I epithelial ovarian cancer, fertility-sparing surgery appears safe overall, although controversy remains in patients with high-risk features (eg, high pathologic grade, clear cell histology, or stage IC disease). In women with low-grade, early-stage endometrial cancer, hormonal therapy has emerged as a viable option. Criteria for patient selection for fertility-sparing therapy are not well defined, thus patients and providers must carefully discuss potential risks and benefits. In general, in carefully selected patients, survival outcomes do not appear to differ significantly between radical and fertility-sparing approaches. Women who undergo fertility-sparing therapies may experience a number of fertility and obstetric complications. Preconception counseling with high-risk obstetric specialists is important to optimize health before a woman attempts to conceive. Identifying appropriate candidates for fertility-sparing treatments, assessing fertility potential, and helping women conceive after cancer treatment is best accomplished through multidisciplinary collaboration between gynecologic oncologists and fertility specialists.

INTRODUCTION

The effect of cancer treatments on fertility and pregnancy outcomes is a distressing concern among the increasing population of reproductive-age women with gynecologic cancer. The 2012–2016 Surveillance, Epidemiology, and End Results (SEER) statistics report 36.5% of cervical cancers, 6.5% of uterine cancers, and 7% of ovarian cancers were diagnosed in women <45 years old. Among gynecologic cancers 44% of women with cervical cancer are diagnosed at an early stage, and almost 70% of endometrial cancers are diagnosed while still confined to the uterus. For ovarian cancer, about 14% are diagnosed with early stage disease only. As women continue to delay childbearing, the number of young women with cancer who face fertility preservation decisions grows. Surgical interventions, gonadotoxic chemotherapy agents, and radiation therapy can have long-term detrimental effects on a woman’s ability to conceive and/or successfully carry a pregnancy. However, fertility preservation techniques have improved over the last two decades, and observational studies have led to careful implementation of a variety of fertility-sparing treatment options for selected reproductive-age women with early-stage gynecologic cancer.

Determining which women with gynecologic cancer are appropriate candidates for fertility-sparing treatments, assessing fertility potential, and helping women conceive after cancer treatment is best accomplished through multidisciplinary collaboration between gynecologic oncologists and fertility specialists. Early involvement of fertility specialists during treatment planning is imperative in optimizing opportunities for counseling and outcomes. In addition, since fertility-sparing cancer treatment can lead to complications that might increase obstetric risks during future pregnancy, a preconception counseling consult with a maternal-fetal medicine specialist is helpful to identify potential problems and strategies to optimize health prior to pregnancy.

Fertility has been reported by patients as one of the most important determinants of their quality of life after treatment. One study found that only 46% of patients with gynecological cancers reported receiving reproductive counseling prior to treatment, consistent with data from similar studies in other cancer types. These data suggest a gap in patient education regarding fertility preservation options, although, reassuringly, rates of fertility preserving surgery in the USA have increased in the past 10 years. The American Society of Clinical Oncology has published guidelines that highlight fertility preservation options as well as the importance of addressing fertility risk and making early referral to fertility specialists prior to initiating cancer therapy. The National Comprehensive Cancer Network (NCCN) has
also included fertility-sparing techniques in published guidelines for cervical, ovarian, and uterine cancer management.

In this article, we review fertility-sparing treatment options and their outcomes for women with cervical, ovarian, and uterine cancer as well as the role of different assisted reproductive technology strategies. We also discuss the safety of assisted reproductive technology in women with a past history of gynecologic cancer.

CERVICAL CANCER

Young women diagnosed with early-stage (International Federation of Gynecology and Obstetrics (FIGO) 2018 IA1-IB1) cervical cancer desiring to preserve their fertility may be candidates for fertility-sparing surgery. The choice of surgery is dependent on clinical presentation and tumor characteristics including stage, tumor size, depth of invasion, and histology. Patients should be counseled that findings during surgery and at pathologic examination might require changes to initial treatment plans that could cause infertility. Magnetic resonance imaging of the pelvis is recommended prior to fertility-sparing surgery to assess size and extent of invasion or spread of the cancer. Findings on imaging may affect the candidacy of patients for fertility-sparing treatment.

Patient Selection and Oncologic Outcomes of Fertility-Sparing Management

Fertility-sparing surgical options for patients with early-stage cervical cancer include cervical conization, simple trachelectomy, and radical trachelectomy. Women with early-stage cervical cancer who may be candidates for fertility-preserving surgery include those with squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma and no evidence of lymph node metastasis. Lymphovascular space invasion is a risk factor for lymph node involvement, but lymphovascular space invasion as a sole finding is not an absolute contraindication to fertility-sparing management. Although primary tumor size >2 cm is not an absolute contraindication to fertility-preserving surgery, a lesion >2 cm is the single most important risk factor for recurrence, regardless of the fertility-sparing surgical approach. These factors and others should be taken into consideration during treatment planning discussions.

Fertility-sparing surgery does not appear to have increased oncologic risks in appropriate candidates, and there has been a recent trend in the use of fertility-sparing surgery for cervical cancer patients. A recent study showed an increase in trachelectomies from 4.6% in 2004 to 17% in 2014 in women under 30 years old. Historically, microinvasive stage IA1 cervical cancer could be treated with fertility-sparing conization and stage IA2-IB1 cervical cancer could be treated with a radical trachelectomy (vaginal, laparoscopic, abdominal, or robot assisted) with pelvic lymph node assessment. Recent data support even more conservative management such as conization and simple trachelectomy with lymph node dissection for patients with IA2-IB1 disease with favorable characteristics. Women with favorable cancer features, including tumor size <2 cm, absence of lymphovascular space invasion, depth of invasion <10 mm, and negative pelvic lymph nodes, have been found to be at very low risk for parametrical involvement, and therefore excellent candidates for more conservative procedures. A systematic review by Bentivegna et al described six fertility-sparing management options and their oncologic outcomes including Dargent’s procedure, simple trachelectomy or cone resection, neoadjuvant chemotherapy followed by conservative surgery, laparoscopic radical trachelectomy, laparoscopic radical trachelectomy, and robot assisted radical trachelectomy. The authors concluded that simple trachelectomy or conization is an option for patients with FIGO 2009 stage IB1 disease <2 cm with or without lymphovascular space invasion. Among 242 patients with stage IB1 cervical cancer who underwent conization or simple trachelectomy, six had a recurrence and one died during the follow-up period of more than 2 years, providing reassurance that these procedures are safe for women with tumors <2 cm. In this study, conization and simple trachelectomy were only considered unsafe in patients with disease >2 cm. Three trials (GOG 278, SHAPE, and ConCerv) will perhaps help solidify the safety of simple trachelectomy or cervical conization with lymph node assessment for these women.

For women with larger tumors, early studies have suggested positive oncologic and reproductive outcomes after neoadjuvant chemotherapy followed by conservative fertility-sparing surgery. In the review by Bentivegna et al, 99 patients were treated with neoadjuvant chemotherapy followed by a fertility-sparing surgical procedure ranging from cold knife cone to radical vaginal trachelectomy. Of these 99 patients, six (6%) had a recurrence with a mean follow-up time of 50 months. The majority of the patients had FIGO 2009 stage IB1 disease, with more than 52 patients with tumors 2–4 cm in size, 25 patients had stage IB2, and three had stage IA1 disease. The authors concluded that neoadjuvant chemotherapy followed by fertility-sparing surgery is a feasible option for patients with up to stage IB2 disease, noting, however, that further data are needed to ensure safety of this approach. The Cervical Cancer Treated with Neoadjuvant Chemotherapy Followed by Fertility-sparing Surgery (CoMeSSa) trial, a single-arm multicenter phase II study, will provide further information regarding the safety of this strategy in this subgroup of patients (tumor size 2–4 cm).

Fertility and Obstetric Outcomes After Fertility-Sparing Surgery

Discussing reproductive outcomes following fertility-sparing therapy is an important part of the treatment planning discussion. One study reported an analysis of 1238 women who underwent a radical trachelectomy (all approaches) for early-stage cervical cancer. Among these women, 469 pregnancies were achieved, with a live birth rate of 67%. Twenty-two percent of the pregnancies ended in first- or second-trimester loss. Of note, in women with lesions >2 cm, the conception rate among women trying to conceive was 24%, compared with 86% of women with lesions <2 cm. A review of abdominal radical trachelectomy found that 67 patients became pregnant of 113 who attempted (59.3%), and at the time of the review, there had been 75 total pregnancies in the group, with a live birth rate of 76% (10 pregnancies were ongoing).

It is important to use caution when interpreting pregnancy and live birth rates based on attempted pregnancies, as there may be significant clinical reasons why a patient who opted for fertility-sparing surgery did not later attempt to conceive. Additionally, it is unclear in many studies whether conceptions were spontaneous or were achieved with the use of assisted reproductive technology. Kim et al found that almost half of successful pregnancies after radical trachelectomy were secondary to assisted reproductive technology. Finally, while reviewing existing data gives an overall
picture of fertility success following conservative surgery, further prospective studies with standardized protocols are necessary to better characterize reproductive outcomes.

Complications after fertility-sparing surgery for cervical cancer such as cervical stenosis and Asherman syndrome—a disease characterized by scar tissue and adhesion formation within the uterus—can negatively impact fertility. Management of postoperative complications may include cervical dilation with or without stent placement for stenosis, and hysteroscopic lysis of adhesions for intrauterine adhesions or Asherman syndrome. Obstetrical complications after trachelectomy include miscarriage, preterm delivery, and preterm premature rupture of membranes. It is important to explain these risks to patients who elect fertility-sparing management and advise consultation with an obstetric specialist prior to conception. Completion hysterectomy after completion of childbearing is not currently recommended, although data are lacking to support this approach. Women should be followed for routine practice surveillance.

OVARIAN CANCER

As mentioned, approximately 7% of epithelial ovarian cancer cases are diagnosed in women younger than 40. Favorable oncologic outcomes in reproductive-age women with early-stage epithelial ovarian cancer have led to evaluation of the feasibility and safety of fertility-sparing procedures in this group.

Patient Selection and Oncologic Outcomes of Fertility-Sparing Management

In a meta-analysis by Bentivegna et al., the authors concluded that fertility-sparing surgery is safe in women with unilateral epithelial cancers who are stage IA grade 1, IA grade 2, and IC grade 1. After the review of existing retrospective studies they concluded fertility-sparing surgery is contraindicated in women with bilateral ovarian involvement, any grade 3 disease, and stages IB, IC2, and IC3. Accruing evidence of the safety of fertility-sparing treatment in women with stage I epithelial ovarian cancer provides reassurance for its routine practice except when it comes to women with high risk features such as high pathologic grade, clear cell histology, and stage IC disease. Melamed et al. analyzed data from the National Cancer Database and identified 1726 women with stage IA and unilateral stage IC epithelial ovarian cancer who underwent fertility-sparing surgery. The probability of survival 10 years after diagnosis was 88.5% in the fertility-sparing surgery group and 89.9% in the conventional surgery group (p=0.3). Two retrospective multi-institutional studies have found similar oncologic outcomes between women with epithelial ovarian cancer who underwent either fertility-sparing or conventional surgery. Kajiyama et al. compared clinical outcomes between 74 patients who underwent fertility-sparing surgery and 498 patients (split into groups <40 years of age and >40 years of age) who underwent conventional surgery for epithelial ovarian cancer. There was no difference in disease-free and overall survival after a median of 66 months. Women who underwent fertility-sparing surgery had an overall survival rate of 90.8%, and women who underwent conventional surgery had overall survival rates of 88.3% (women <40 years old) and 90.6% (women >40 years old) (p=0.8). Disease-free survival rates for these groups were 87.9%, 84.4%, and 85.3%, respectively (p=0.7). Fruscio et al. compared 242 women who underwent fertility-sparing surgery with 789 patients who underwent conventional surgery for epithelial ovarian cancer and found that survival was similar between the groups after >11 years of follow-up.

In a retrospective study, Morice et al. found that all three patients with stage IC epithelial ovarian cancer who underwent fertility-sparing surgery experienced recurrence. Furthermore, a Japanese multi-institutional study by Satoh et al. raised concerns regarding the safety of fertility conservation in women with grade 3 tumors. Women with stage IA grade 3 tumors (n=3) had a 5 year recurrence-free survival rate of 33.3% compared with 97.8% in women with stage IA disease with favorable histology (n=108) and 100% in women with stage IA clear cell disease (n=15). The number of women in the study with grade 3 disease was much lower than the other groups, likely because these women are often counseled against fertility-sparing management. Patients who desire fertility-sparing treatment should clearly understand that data regarding outcomes are limited, particularly among those patients with high-risk features.

Non-epithelial cancers of the ovary, including malignant germ cell tumors and ovarian sex-cord-stromal tumors, each account for approximately 5% of all ovarian malignancies. Ovarian germ cell tumors commonly occur in reproductive-age women, and whenever feasible, fertility-sparing surgery is considered standard because these tumors are extremely chemosensitive. Sex cord-stromal tumors of the ovary may occur at any age but are most commonly observed in postmenopausal women. The most common histology is granulosa cell tumor, which generally has an indolent course. Fertility-sparing surgery is possible in a high percentage of young patients with sex-cord-stromal tumors.

Fertility and Obstetric Outcomes After Fertility-Sparing Surgery

Any surgery that involves removal of ovarian tissue may impact both immediate and long-term ovarian reserve, requiring some women to undergo ovarian stimulation with either oral agents or injectable gonadotropins in order to ovulate and achieve pregnancy. However, spontaneous conceptions have also been reported. Data on outcomes after fertility-sparing surgery in women with epithelial ovarian cancer show an approximately 30% rate of successful conception in this population; however, when findings are adjusted to only include women of reproductive age, rates of successful conception increase to 66–100%. In a review of 440 patients who underwent fertility-sparing surgery for early epithelial ovarian cancer, 127 (29%) women successfully conceived. Many of the studies included in this review reported patient’s desire to conceive, and of those 128 women, 90 (70%) achieved a pregnancy. Unfortunately there were few studies that reported whether or not pregnancies were achieved by assisted reproductive technology, leaving gaps in assessment of the data. Another review of fertility outcomes following conservative treatment of early stage ovarian cancer reported that 262 (37%) women out of 711 successfully conceived. Only 233 of these women had epithelial ovarian cancer, but the treatment across all patients was most commonly unilateral oophorectomy with or without chemotherapy.

Some women who undergo fertility-sparing surgery subsequently undergo assisted reproductive technology because of...
reduced ovarian reserve. To date, more than 220 pregnancies have been reported after fertility-sparing surgery for ovarian cancer, with an overall miscarriage rate of 17%. Similarly to cervical cancer, pregnancy rates after fertility-sparing treatment for ovarian cancer must be interpreted with caution since findings may be confounded by women’s decisions to conceive or not.

Despite the risk of ovarian dysfunction among patients with germ cell tumors who receive chemotherapy, many of these patients maintain reproductive potential following treatment. A review of 658 patients from six studies found that 149 patients (22.6%) conceived after fertility-sparing surgery; however, when the analysis was limited to women who attempted conception, the rates of pregnancy in individual studies were much higher, ranging from 66–95%, consistent with fertility rates reported in other studies. A more recent review of 105 patients with malignant ovarian germ cell tumors showed a 93% pregnancy rate among the 45 patients who attempted to conceive, seven of whom sought fertility treatment. The live birth rate of these pregnancies was 86%. As mentioned above, caution should be used when interpreting pregnancy rates based only on women who attempted conception.

UTERINE CANCER

Hormonal therapy has emerged as a viable treatment option in women with low-grade, early-stage endometrial cancer. The safety and efficacy of hormonal therapy has been described, and investigation continues to better define and standardize treatment regimens. Fertility-sparing therapy includes progestin administration, either orally or locally, through a progestin-releasing intrauterine device. If diagnostic workup leads to a recommendation for hysterectomy, ovarian preservation at the time of surgery may be considered, as well as referral to a reproductive endocrinologist for discussion of assisted reproductive technology and third-party reproduction.

Patient Selection for Fertility-Sparing Therapy

As more young women are diagnosed with endometrial cancer and the safety of fertility-sparing treatment continues to be assessed, many may seek fertility-sparing options. Between 2000 and 2014, there was an almost 10% increase in patients diagnosed with endometrial cancer who were treated with progesterone alone; almost 25% of patients with endometrial cancer in 2014 were treated with progesterone, either alone or eventually followed by hysterectomy. For patients who desire fertility preservation, magnetic resonance imaging is recommended to evaluate the depth of myometrial invasion and distant spread. Additionally, a more reliable method of endometrial sampling such as dilation and curettage should be used to more accurately assess tumor grade.

In general, fertility-sparing therapy is indicated only in patients with grade 1 non-invasive endometrial cancer, although some patients with grade 2 disease or myometrial invasion <50% may be eligible under research protocols and after thorough counseling about the higher risk of non-response, worsening disease, and recurrence. Patients with known insulin resistance have been shown to require longer duration of treatment to achieve complete response. Body mass index >25 kg/m² has also been associated with failure to achieve complete response, longer duration of therapy to achieve complete response, and increased rates of recurrence. Patients with these comorbid conditions should be counseled about the risks of treatment failure as well as lifestyle changes to implement during treatment if they choose to proceed. Importantly, for all women treated with hormonal therapy, the risk of recurrence is significant even after complete response, and hysterectomy after completion of childbearing is recommended.

Oncologic Outcomes of Hormonal Therapy

Existing data on the efficacy of progestin therapy predominantly comes from small studies with highly variable response rates reported. Studies have included different doses, agents, and regimens of hormones. Most of the studies of hormonal therapy for women with endometrial cancer have evaluated oral progestins, and we found no studies that directly compared oral progestins with a progestin-releasing intrauterine device. A meta-analysis of 45 studies that included 391 patients reported an overall response rate of 78% with a complete response rate of 53%. The exact duration of therapeutic benefit from hormonal therapy is unknown, and even patients who initially respond are at significant risk for recurrence. In the meta-analysis, the risk of recurrence ranged from 14% in women with endometrial hyperplasia to 25% in women with carcinoma during the 39 month period studied. Although there is no standard follow-up protocol, patients with uterine cancer treated with primary hormonal therapy should typically be re-examined every 3–6 months with endometrial sampling. There is no consensus on exact duration of treatment; however, most studies thus far have found 3 months to be necessary for regression with a median time to regression of 4 to 6 months. Presence of risk factors such as obesity and insulin resistance may prompt providers to allow a longer treatment time. Additionally, preliminary evidence supports that women who relapse after complete response may be candidates for a second course of hormonal therapy with good response. Wang et al found no statistically significant difference in complete response rates between primary treatment and women who were treated with hormonal therapy a second time following recurrence (94.7% and 82.6%, respectively, p=0.05), although more robust data are needed to support this finding. As emphasized previously, this information should be used to guide informative and collaborative discussions with patients, taking into account their unique oncologic situation and reproductive goals, to create a treatment plan that is both safe and acceptable to the patient.

Fertility and Obstetric Outcomes after Hormonal Therapy

A systematic review by Gunderson et al summarized reproductive outcomes from 38 studies of women with complex atypical hyperplasia and grade I endometrial cancer who underwent various regimens of hormonal therapy. Of 315 women, 114 (36%) achieved pregnancy, 41% of women with complex atypical hyperplasia and 35% of women with endometrial carcinoma. From these 114 pregnancies, 117 live births occurred. However, information regarding attempted pregnancy was not available from the included studies. A separate systematic review by Gallos et al of 34 studies of fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia, including 451 women, showed that 142 women underwent assisted reproductive technology to conceive, of whom 56 women (39.4%) had at least one live birth. Of the remaining 309 women, who were assumed to have attempted conception naturally, 46 women (14.9%) achieved at least one live birth.
Despite successful hormonal treatment of endometrial cancer, many young women still face subfertility due to underlying metabolic disorders, such as polycystic ovary syndrome. These women often have a reduced rate of conception and live birth, possibly due to factors that also contributed to the development of endometrial cancer (eg, chronic anovulation and/or obesity). Further, their endometrial pathology both before and after treatment may not promote embryonic implantation and development. Consultation with a fertility specialist during the treatment course allows patients to take advantage of that time to optimize health status with lifestyle interventions (diet, exercise, and weight loss) and correct metabolic derangements such as hyperinsulinemia through use of oral insulin-sensitizing agents such as metformin. For women who are severely obese with multiple comorbidities, bariatric surgery can be considered. A recent meta-analysis demonstrated that among women with a history of endometrial cancer, those who pursued assisted reproductive technology had significantly higher pregnancy rates than those who did not, regardless of their initial diagnosis. It is recommended that assisted reproductive technology be started as soon as response to hormonal therapy is achieved, to maximize pregnancy success and minimize time prior to definitive surgery with hysterectomy and thereby minimize the risk of relapse. Ultimately, immediate assisted reproductive technology helps to avoid prolonged, unopposed estrogen stimulation, which could also result in relapse and disease progression.

ASSISTED REPRODUCTIVE TECHNOLOGY AND OTHER METHODS FOR PRESERVATION OF FERTILITY

In some instances, an “early” gynecologic cancer is found to be more invasive or aggressive than originally thought. For women with gynecologic cancer who will ultimately receive gonadotoxic chemotherapy and/or pelvic/abdominal irradiation, the standard of care for fertility preservation is the use of assisted reproductive technology. In the USA, standard assisted reproductive technology interventions include oocyte cryopreservation and embryo cryopreservation prior to initiation of cancer treatment. Ovarian tissue cryopreservation is readily available worldwide but remains experimental in the USA; this procedure is ideal for prepubertal girls needing fertility preservation and women who have contraindications to or lack time to pursue assisted reproductive technology. Experimental options include the use of fertility protective agents during chemotherapy and ovarian transposition during pelvic or abdominal irradiation. Women who conceive after radiation therapy are at risk for miscarriage, preterm labor, and preterm birth. Many women with a history of uterine irradiation will be counseled to consider using a gestational carrier to minimize these risks. While newer proton beam or other focused radiation techniques offer promise in preserving ovarian and uterine function, data on the impact of these techniques on fertility are lacking.

Oocyte Cryopreservation and Embryo Cryopreservation

For oocyte preservation, a woman undergoes controlled ovarian hyper-stimulation using injectable gonadotropins to recruit multiple follicles. Frequent ultrasound studies, typically every 1–2 days, and measurements of serum hormone levels are used to assess response to medications and tailor therapy to maximize benefit. When the follicles have reached optimal size, maturation is induced by giving a trigger injection, typically human chorionic gonadotropin, gonadotropin-releasing hormone (GnRH) agonists, or a combination of both medications. Approximately 36 hours later, oocytes are aspirated from the follicles transvaginally under ultrasound guidance. Oocytes can be frozen at this point, or if the patient chooses to freeze embryos, the oocytes are inseminated with sperm and the resultant embryos are cultured and frozen. One of the greatest risks of assisted reproductive technology, specifically in younger patients with good ovarian reserve who pursue oocyte/embryo cryopreservation, is the risk of ovarian hyperstimulation syndrome, which can be life-threatening in severe cases and potentially delay initiation of cancer treatment.

Currently, both oocyte cryopreservation and embryo cryopreservation are established fertility preservation options. The experimental status of oocyte cryopreservation was lifted in 2013 when evidence that fertilization and pregnancy rates with use of thawed cryopreserved oocytes were similar to those after in vitro fertilization, and intracytoplasmic sperm injection using fresh oocytes became available. Clinical pregnancy rates per thawed oocyte range from 4.5–12% depending on age. Overall, oocytes survive vitrification at a rate of 90–97%, and fertilization rates are usually >70%. Previous studies have shown no difference in live birth rates between women who conceive using thawed cryopreserved oocytes and age-matched women who conceive using assisted reproductive technology with fresh oocytes; however, a more recent study suggests that cryopreserved eggs may yield a 10% lower live birth rate than fresh eggs. Survival rates per thawed embryo range from 35–90% and implantation rates range from 8–30%, with cumulative pregnancy rates above 60%.

Ovarian Tissue Cryopreservation

For ovarian tissue cryopreservation, an ovary or a portion of an ovary is removed surgically (usually along with other necessary surgical procedures such as port placement), and the cortex is dissected off and cut into strips. These strips of cortical tissue are cryopreserved and re-implanted if a patient has ovarian failure and childbearing is desired. The tissue is re-implanted either in the pelvic cavity, typically directly onto the ovary or in the ovarian fossa (orthotopic), or at a distant site in the body (heterotopic). This process is typically completed in a minimally invasive fashion (laparoscopically or robotically), with the hope that the re-implanted tissue will regain ovarian hormonal function leading to ovulation of a mature oocyte. More than 100 births following ovarian tissue cryopreservation and re-implantation have been reported in the literature to date. Benefits of ovarian tissue cryopreservation are that it is quick, requires minor surgery that can be completed with other surgical procedures, does not require hormonal stimulation, and it can potentially restore normal hormonal function. A major risk is that for certain types of cancer, such as leukemia, the procedure could reseed the body with unrecognized malignant cells.

Use of GnRH Agonists

Experimental fertility protecting agents can be used when the above options are not clinically feasible or are not desired by the patient. The proposed mechanisms of action of GnRH agonists include protection of existing follicles from destruction during chemotherapy by suppressing gonadotropin levels, reducing perfusion of ovarian tissue, and other unknown mechanisms. However, some of these theories have been criticized as lacking biological plausibility, as primordial follicles do not express gonadotropin or GnRH receptors and therefore...
are not affected by changes in GnRH levels. Additionally, it has been shown that gonadotoxic agents induce primordial follicle death via DNA breaks in oocytes, and GnRH agonist’s mechanism of action does not directly inhibit this process.\textsuperscript{43} Data on the efficacy of the use of GnRH agonists are mixed and controversial, especially since existing studies are confounded by varying definitions of ovarian insufficiency/failure, patient demographics, length of follow-up, and dosing parameters. The use of GnRH agonists during cancer treatment may have other benefits, such as reducing vaginal bleeding in patients with treatment-induced thrombocytopenia or pancytopenia. However, due to a lack of evidence of efficacy for fertility preservation, the American Society of Clinical Oncology recommends that ovarian suppression remains experimental and that it not be used in place of proven fertility preservation methods.\textsuperscript{7}

**Ovarian Transposition Before Pelvic or Abdominal Irradiation**

For women who will receive gonadotoxic doses of radiation to the abdomen and pelvis and who do not want to pursue oocyte cryopreservation prior to treatment, ovarian transposition can be considered. In this procedure, the ovaries are surgically moved outside the radiation field. This may allow preservation of ovarian function after therapy in 65–90% of women.\textsuperscript{44} With ovarian transposition, however, the uterus remains unprotected from radiation, and the potential impact of uterine irradiation on the likelihood of a future pregnancy must be considered.\textsuperscript{45} Recently, laparoscopic uterine transposition of the uterus to the upper abdomen has been reported with preliminary success, and this method may serve as a possible viable option for uterine protection for such patients.\textsuperscript{46}

A recent systematic review and meta-analysis studying the outcomes of ovarian transposition in women with gynecologic cancers provided insight into the efficacy of this treatment option. The review included 24 articles including almost 900 women undergoing ovarian transposition. In women who had transposition alone, 90% had preservation of ovarian function (95% confidence interval (CI) 92% to 99%), and none of the patients suffered metastases to transposed ovaries. In women undergoing brachytherapy along with ovarian transposition, 94% had preservation of ovarian function (95% CI 79% to 111%). Similarly, in women who underwent external beam radiotherapy and ovarian transposition, 65% had preservation of ovarian function (95% CI 56% to 74%). Potential complications associated with ovarian transposition include symptomatic ovarian cysts, metastases to the ovaries from the primary site, or diminished ovarian reserve due to impact on ovarian blood supply from surgical manipulation and transposition. Oocyte retrieval can be performed on these patients, however, but may require abdominal retrieval for successful completion.\textsuperscript{44}

**ONCOLOGIC SAFETY OF ASSISTED REPRODUCTIVE TECHNOLOGY IN WOMEN WITH A HISTORY OF GYNECOLOGIC CANCER**

An important concern for women with a history of gynecologic cancer considering assisted reproduction is the impact of assisted reproductive technology on the risk of cancer recurrence. We are aware of only one study that directly examined the risk of gynecologic cancer recurrence following assisted reproductive technology: a review of 36 patients with a history of endometrial cancer that found no significant increase in the rate of recurrence following assisted reproductive technology.\textsuperscript{47} Given that only this one study directly examined assisted reproductive technology in gynecologic cancer survivors, the impact on recurrence risk has to be estimated from studies comparing cancer rates in women without a prior cancer history who did and did not undergo assisted reproductive technology. Most studies have not shown an increased risk of cancer in women with prior use of assisted reproductive technology compared with the general population; however, the studies are few and often limited by the constraints of information available in large databases with short-term follow-up.\textsuperscript{48}

There is concern about the effects of ovarian hyperstimulation in women with estrogen-sensitive cancers. The use of selective estrogen receptor modulators and aromatase inhibitors has been shown to reduce estradiol levels without compromising assisted reproduction outcomes. Several studies have reported no increased risk of breast cancer in women following assisted reproductive technology. Patients also appear to be at no increased risk for ovarian, cervical, or endometrial cancers given existing data.\textsuperscript{48} In a Cochrane review of 25 studies and over 180,000 women, five studies were identified that reported an increased risk of ovarian cancer in women who had undergone assisted reproductive technology. However, after quality assessment of these studies, the authors concluded that there appeared to be no increased risk of ovarian cancer in women with a history of infertility treatment.\textsuperscript{49}

Several factors complicate research exploring cancer development or recurrence after assisted reproductive technology. Risk factors for infertility and gynecologic cancers often overlap, making it difficult to assess causation in the relationship between assisted reproduction and cancer development. The field of assisted reproductive technology continues to evolve at a fast pace, making evaluation of long-term outcomes a challenge as well.\textsuperscript{48} Quantification of risk should be individualized, and further prospective studies are necessary to better ensure the safety profile of assisted reproduction in women with a history of gynecologic cancer.

**CONCLUSIONS**

As women postpone childbearing, fertility-sparing treatments have become more frequent among patients with gynecologic cancers. In the absence of randomized trials, observational studies have driven the cautious consideration of fertility-sparing treatments in selected patients with certain malignancies. Most studies of pregnancy outcomes among women with gynecologic cancers have been small series from academic centers with limited numbers of patients. Pregnancy rates among cancer survivors are generally lower than those of age-matched peers.\textsuperscript{36} This difference may reflect both higher rates of infertility and reduced attempts at conception among cancer survivors. Information regarding the success of assisted reproductive technology in women with gynecologic cancer is limited. Further studies are needed to better establish the effects of assisted reproductive technology on oncological outcomes, including those in women who never achieve pregnancy.

**Contributors** Each of the authors contributed to the planning, writing, and editing of this article in an equal manner.

**Funding** National Institutes of Health, National Cancer Institute, grants K08CA234333 and P30CA016672.

**Competing interests** None declared.

**Patient consent for publication** Not required.
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