Oncofertility: An Emerging Discipline in Obstetrics and Gynecology

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Oncofertility is an exciting new interdisciplinary field that encompasses the obstetrician gynecologist, gynecologic oncologist, reproductive endocrinologist, and primary care physician in a common goal to provide fertility preservation options for cancer patients. Maintaining their fertility is of the upmost importance for many oncology patients diagnosed during their childbearing years. This review addresses the common types of cancers in reproductive-age patients and how the treatment of these cancers may impact reproductive potential. Fertility preservation treatments will also be discussed to assist health care providers in appropriately counseling patients about options after a diagnosis of cancer. The goal of oncofertility is to provide both physicians and patients with the knowledge and resources to make fertility an ongoing opportunity for all patients who desire a future with children.

Target Audience: Obstetricians and gynecologists, medical/surgical oncologists, family physicians

Learning Objectives: After completing this CME activity, physicians should be better able to manage patients with gynecological cancers, evaluate the impact of cancer treatment on fertility, and counsel patients regarding potential fertility-sparing treatment options.

Oncofertility was established as a new discipline in the field of obstetrics and gynecology in 2006, developed for the express purpose of preserving, expanding, and restoring the reproductive future of cancer patients whose treatment may have compromised their fertility.1 Oncofertility as a discipline has far-reaching implications in regard to the treatment of a malignancy and the preservation of fertility and spans to all subspecialties of oncology. It can be a vital aspect of a patient’s oncologic care, whether male or female, and regardless of whether the patient has reached his/her reproductive potential. This review addresses the common types of cancers in reproductive-age patients and how the treatment of these cancers may impact reproductive potential. Fertility preservation treatments will also be discussed to assist health care providers in appropriately counseling patients about options after a diagnosis of cancer.

Cancer statistics alone serve to illustrate the need for oncofertility in our medical community. Currently, approximately 1 in 400 adults is a cancer survivor. In 2009, approximately 68,400 adolescents and young adults aged 15–39 years were diagnosed with a malignancy, making cancer the leading cause of disease-related deaths in that age group.2 In fact, by the year 2030, there will be an anticipated 50% increase in the number of patients with a diagnosis of cancer. Approximately 45% of those patients will be females, and 10% of those females will be diagnosed with a gynecologic malignancy at some point during their lives.3

Why is oncofertility just coming to the forefront of oncology care? As the pace of basic science and clinical research progress forward at an astounding
rate, the medical community finds itself able to diagnose some malignancies earlier and with less-invasive methods. Improved drug development protocols and the development of targeted biologic agents allow for improved outcomes in disease-free survival and overall survival rates. The advent of minimally invasive surgery has also granted surgeons the opportunity to give their patients a “low-impact” approach to surgical therapy, allowing for a quicker recovery time and return to normal activity.

Fertility preservation options in various forms have been available to the medical and surgical oncology community for many years. However, studies have shown that oncologists infrequently discuss fertility preservation options with their patients or refer their patients to reproductive endocrinologists/infertility specialists. Typically, the top priority of the oncologist is to treat the cancer. Physicians and patients themselves may be very hesitant to delay treatment for any reason, and there is certainly the potential for delay while referrals are placed or fertility preservation options are explored. Oncologists have also been wary to introduce a topic that may add stress to a patient’s already critical situation, especially if the cancer type and stage carry a poor prognosis. Also, any number of religious, language, cultural, or gender barriers may prevent fertility preservation options from being discussed with the patient in a timely fashion. In addition to those factors, for many physicians there is a lack of training in fertility-sparing surgical procedures or awareness of new options for fertility preservation before, during, or after treatment is complete.

Maintaining their ability to bear children is of the utmost importance for many patients diagnosed with a malignancy during their fertile years. Noyes et al. stated that 55% of patients felt that having a child was the most important event in their life, whereas 64% of oncology patients cited the impact of cancer treatment on their fertility as the most concerning issue regarding their treatment. The possibility of reproductive dysfunction as a result of cancer therapy is a known stressor, and the loss of fertility during cancer treatment has been shown to result in increased depressive and posttraumatic stress disorder symptoms, more severe menopausal symptoms, sexual dysfunction, and a lower overall physical quality of life.

THE IMPACT OF CANCER TREATMENT ON FERTILITY

The effects of radiotherapy and chemotherapy can be devastating on the systems vital to the ability to conceive. Radiotherapy and chemotherapy can impact fertility not only at the uterus and ovary, but also along the entire hypothalamic-pituitary axis. A functioning neuroendocrine system regulates the menstrual cycle, allowing for ovulation and maintenance of an early pregnancy. The hypothalamic-pituitary axis regulates the menstrual cycle, ovulation, and, ultimately, pregnancy. Healthy pools of ovarian follicles produce mature gametes with the potential for fertilization, whether that is spontaneous fertilization or via artificial reproductive technology (ART). Although the uterus does not play a true endocrine role in the process of ovulation and conception, it must support implantation and development of a pregnancy to viability and to term.

Studies have shown that there are several predictive factors of the impact cancer treatment can have on fertility. The age of the patient and her fertility status before treatment are possibly the greatest predictive factor on posttreatment fertility options. Ovarian reserve is a term used to describe a woman’s fertility potential based primarily on indirect evaluation of the quantity of oocytes remaining in the ovaries. Individual ovarian reserve varies significantly among the healthy population and has a significant impact on the potential for future fertility and ovarian stimulation and future assisted reproductive technologies (ART). Pelvic radiation and chemotherapy may both decrease ovarian reserve by directly depleting the pool of viable oocytes. Several modalities have been evaluated as markers of ovarian reserve including cycle days 2 to 3 follicle-stimulating hormone (FSH), antimüllerian hormone (AMH), and ovarian ultrasound of antral follicles (AFCs). Anti müllerian hormone may be drawn at any point in the menstrual cycle in contrast to FSH testing, which must be performed on cycle days 2 to 4. Anti müllerian hormone is also not influenced by other hormone use such as oral contraceptive pills. Therefore, these advantages make it appealing as a tool to assess ovarian reserve.

Assessment of a patient’s ovarian reserve before and after cancer treatment may provide valuable information for counseling patients of fertility-preserving options before treatment and future fertility after treatment. A study in premenopausal women receiving chemotherapy reported that pretreatment FSH, AMH, and AFC all were found to reflect future ovarian activity for women with menses after chemotherapy, but AMH was the most predictive. Further research is needed to determine the impact of cancer treatments on markers of ovarian reserve and any correlation with future fertility. A summary of markers of ovarian reserve is provided in Table 1. It
is important to note that markers of ovarian reserve have been studied primarily in the general infertility population. The sensitivity and specificity were determined based on evaluating the ovarian response to fertility medications and subsequent pregnancy in patients treated with in vitro fertilization (IVF). Research in cancer patients is ongoing to determine if these markers may be predictive of ovarian function or future pregnancy after chemotherapy (Table 1).

**Radiation Therapy**

Radiation is typically administered as external beam therapy (teletherapy), intracavitary (brachytherapy), or total body irradiation as is utilized with stem cell transplantation. The effects of radiation therapy are dependent on the dose and the field applied. Radiation is typically targeted at the affected area; however, the impact of scattered radiation during treatment may also affect reproductive potential. Total body irradiation, used in stem cell transplantation, has greater than 80% risk of ovarian oocyte depletion with subsequent permanent amenorrhea.

Ovarian follicle destruction leads to gamete loss, impaired hormone function, and even possibly uterine dysfunction. Limited field external beam radiation has a reduced risk of ovarian or uterine damage depending on the location, dose, fractionation schedule, and age of the patient at the time of radiation treatment. In a study of 2000 women treated with pelvic radiotherapy, 95% had permanent ovarian failure following radiotherapy of 5 to 105 Gy. It was reported that radiation doses greater than 5 Gy for women older than 30 years results in permanent amenorrhea; however, a more recent report found that the lethal dose (LD50) of the human oocyte is actually less than 2 Gy. Data from the Childhood Cancer Survival Study revealed that exposure of the ovaries to high-dose radiation (>20 Gy) results in amenorrhea for 70% to 80% of patients, but the rate of amenorrhea at lower radiation doses is dependent on patient age. Patients exposed to 10 Gy of radiation or less had approximately a 5% rate of amenorrhea if they were younger than 13 years at the time of treatment, but it increased to approximately 25% if they were aged 13 to 20 years.

It has been established that cranial radiation can result in altered hypothalamic and pituitary function, affecting secretion of gonadotropin-releasing hormone (GnRH) and prolactin, which ultimately affect secretion of terminal hormones including FSH, lutetizing hormone (LH), estradiol, and progesterone. High-dose cranial radiation greater than 24 Gy can result in delayed puberty or amenorrhea in young females.1,9 The uterus itself is rarely affected by traditional chemotherapy; however, the effects of radiotherapy can be significant. Radiation levels between 14 and 30 Gy have been shown to result in decreased volume, elasticity, and vasculature. The total of these effects directly damages the endometrium and myometrium, which correlates with an increased incidence of miscarriage, placental abnormalities, preterm birth, and low birth-weight infants.1,4,8

**Chemotherapy**

Ovarian damage secondary to chemotherapy is drug and dose dependent and is related to the patient’s age at the time of treatment with progressively smaller doses required to produce ovarian failure with increasing age (Table 2). The primary impact of chemotherapy on fertility is related directly to the loss of ovarian function secondary to the gonadotoxicity of many chemotherapeutic agents. Cell-cycle, nonspecific alkylating agents such as cyclophosphamide destroy resting primordial oocytes, whereas antimetabolite agents (methotrexate) have limited effects on ovarian function. The greatest risk is in women older than 40 years receiving alkylating agents, with up to 80% of patients having permanent amenorrhea after treatment. However, in women younger than 30 years, the risk of permanent amenorrhea is substantially decreased to less than 20%. The effect of chemotherapy will also depend on whether it is radical or adjuvant, or single agent or combination. Fortunately, the more recent ABVD

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**TABLE 1**

<table>
<thead>
<tr>
<th>Test</th>
<th>Cutpoint</th>
<th>Reliability</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH, IU/L</td>
<td>10-20</td>
<td>Limited</td>
<td>Widespread use</td>
<td>Reliability, high specificity, but low sensitivity for ovarian response or pregnancy</td>
</tr>
<tr>
<td>AMH, ng/mL</td>
<td>0.2-0.7</td>
<td>Good</td>
<td>Reliability, can be obtained any day of the menstrual cycle</td>
<td>Limit of detectability; cutpoints fairly specific for poor ovarian response, but limited data on pregnancy</td>
</tr>
<tr>
<td>AFC</td>
<td>3-10</td>
<td>Good</td>
<td>Reliability, widespread use</td>
<td>High specificity, but low sensitivity for ovarian response or pregnancy</td>
</tr>
</tbody>
</table>
(doxorubicin, bleomycin, vincristine, and dacarbazine) regimen used in the treatment of Hodgkin disease is significantly less toxic to the ovaries than the older MOPP (mechlorethamine, vincristine, procarbazine, and prednisolone) regimen. The classic CMF (cyclophosphamide, methotrexate, 5-fluorouracil) regimen for breast cancer will result in greater than 70% amenorrhea rates for women older than 40 years. The newer taxanes are still being evaluated for their impact on fertility in human subjects but ideally will be less gonadotoxic than currently used regimens.

Unfortunately, estimates on the impact on fertility vary widely and depend on various factors. Permanent amenorrhea was defined as lack of menses 12 months after chemotherapy, but duration of amenorrhea was not defined in all retrospective studies. Table 3 reflects current figures regarding the likelihood of amenorrhea depending on specific chemotherapy regimens. Although the rates of amenorrhea vary between studies and regimens, there is a clear relationship between increasing age and risk of subsequent amenorrhea. However, aside from patient age, there is no definitive predictor before treatment, making counseling on future fertility challenging for health care providers.

**TABLE 3**
Chemotherapy Regimens and Risk of Amenorrhea

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Age &lt;30 y</th>
<th>Age 40-45 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0</td>
<td>10-20%</td>
</tr>
<tr>
<td>CMF × 6</td>
<td>&lt;5%&lt;sup&gt;18&lt;/sup&gt; 19%&lt;sup&gt;22&lt;/sup&gt;</td>
<td>10%&lt;sup&gt;-&lt;/sup&gt;-40%&lt;sup&gt;18&lt;/sup&gt; 38%&lt;sup&gt;20&lt;/sup&gt; 31%&lt;sup&gt;21&lt;/sup&gt; 94%&lt;sup&gt;21&lt;/sup&gt;</td>
</tr>
<tr>
<td>CEF × 6</td>
<td>&lt;5%&lt;sup&gt;18&lt;/sup&gt; 19%&lt;sup&gt;22&lt;/sup&gt;</td>
<td>10%&lt;sup&gt;-&lt;/sup&gt;-40%&lt;sup&gt;18&lt;/sup&gt; 38%&lt;sup&gt;20&lt;/sup&gt; 31%&lt;sup&gt;21&lt;/sup&gt; 94%&lt;sup&gt;21&lt;/sup&gt;</td>
</tr>
<tr>
<td>FEC × 6</td>
<td>—</td>
<td>34%&lt;sup&gt;23&lt;/sup&gt; 96%&lt;sup&gt;23&lt;/sup&gt;</td>
</tr>
<tr>
<td>3FEC/3D</td>
<td>—</td>
<td>40%&lt;sup&gt;23&lt;/sup&gt; 81%&lt;sup&gt;23&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

CEF indicates cyclophosphamide, epirubicin, 5-fluorouracil; FEC, fluorouracil, epirubicin, cyclophosphamide; 3FEC/3D, fluorouracil, epirubicin followed by docetaxel (3 cycles each).

CANCER IN THE FERTILE POPULATION

Physicians who diagnose any patient with a malignancy during their reproductive years should address the issue of potential loss of fertility before initiation of cancer treatment. Fertility preservation should be recommended to all patients whose risk of infertility after treatment is greater than 30%. Sperm cryopreservation should be offered to all male cancer patients who may experience oligospermia or azoospermia after receiving gonadotoxic agents, whereas hormonal function of the Leydig cells is usually not affected until a higher cumulative dose of therapy. The treatment of Hodgkin lymphoma has been modified in recent years as previous use of alkylating agents such as procarbazine and cyclophosphamide results in significant azoospermia. Treatment with ABVD, which uses no alkylating agents, results in significantly less gonadotoxicity and no patients with permanent azoospermia.

**Cancer Treatment and Testicular Function**

The major functions of the male reproductive tract involve the manufacturing and delivery of spermatozoa to the female and production of male sex steroid hormones. Spermatogenesis involves the proliferation and differentiation of diploid germ cell spermatogonia into mature haploid spermatozoa. Anterior pituitary hormones, FSH and LH, regulate testicular function and are under the influence of GnRH, which in turn is controlled by feedback from testicular hormones inhibin and testosterone.

The testis, in both prepubertal and sexually mature males, can be significantly affected by both radiation and chemotherapy. The germ cells of the testis are quite sensitive to radiation, with doses as low as 0.1 to 1.2 Gy impairing spermatogenesis, whereas doses greater than 4 Gy result in irreversible azoospermia. The somatic cells, or Leydig cells, are more resistant. Cell dysfunction is not apparent until doses of 20 to 30 Gy have been administered, which occurs in treatment of leukemia for local infiltration or total body irradiation in preparation for bone marrow transplantation.24

The germ cells of the testis are very chemosensitive irrespective of the stage of pubertal development. Patients may experience oligospermia or azoospermia after receiving gonadotoxic agents, whereas hormonal function of the Leydig cells is usually not affected until a higher cumulative dose of therapy. The treatment of Hodgkin lymphoma has been modified in recent years as previous use of alkylating agents such as procarbazine and cyclophosphamide results in significant azoospermia. Treatment with ABVD, which uses no alkylating agents, results in significantly less gonadotoxicity and no patients with permanent azoospermia.
patients of reproductive age regardless of the risk of gonadal failure, as sperm cryopreservation is a well-established noninvasive or minimally invasive fertility preservation technique. Fertility preservation in the female population is far more complex and may depend on the patient age, urgency of treatment, and the regimen and dosage of treatment. The most common cancers in reproductive-age women are breast, melanoma, cervical cancer, non-Hodgkin lymphoma, and leukemia. The 5-year female cancer survival is dependent on stage at diagnosis but is currently 90% for breast, 91% for melanoma, 71% for cervical, 69% non-Hodgkin lymphoma, and 55% for leukemia at first diagnosis. Each patient desiring fertility preservation must have a coordinated multidisciplinary approach to his/her care. The specific implications of malignancies such as breast cancer, hematologic cancers, gynecologic cancers, and male testicular cancers are discussed at length below.

Breast Cancer and Fertility

In 2011, more than 230,000 women were diagnosed with breast cancer, and approximately 11,000 were younger than 40 years. For those women desiring future fertility, chemotherapy-dependent gonadal toxicity is dependent on patient age and the dose and number of alkylating agents. When appropriate for the diagnosis and stage of breast cancer, the administration of chemotherapy has been shown to reduce the risk of recurrence and death by a relative factor of 50%. There have been considerable and recent developments in ART for breast cancer patients. Until recently, preserving oocytes or embryos required a delay in cancer treatment of up to 4 to 6 weeks to complete the IVF cycle. Traditional ovarian preparation for IVF required 10 to 14 days of ovarian stimulation with exogenous gonadotropins followed by GnRH agonists for approximately 2 weeks to prevent premature ovulation. Gonadotropin-releasing hormone agonists were initiated in the luteal phase of the cycle, and this may add up to 3 additional weeks to the time required for oocyte retrieval, depending on when the patient presents for treatment.

Recent advances including the development of GnRH antagonists have significantly decreased the interval from patient presentation to gamete cryopreservation. In contrast to GnRH agonists, GnRH antagonists immediately suppress pituitary release of FSH and LH and do not require the 10 to 14 days of administration before gonadotropin initiation. Gonadotropin stimulation begins on days 2 to 3 of a menstrual cycle, and GnRH agonists are started approximately 6 days later. This approach requires awaiting menses before initiating gonadotropins but decreases the interval to oocyte retrieval compared with traditional IVF stimulation protocols.

A recent report of 3 patients initiating “random start IVF” evaluated the effectiveness of initiating GnRH antagonists at the time of patient presentation (menstrual cycle days 11, 14, and 17) rather than waiting for menses. This was then followed by the standard 10 to 14 days of ovarian stimulation and subsequent oocyte retrieval. The goal was to decrease the time to oocyte retrieval for breast cancer patients and resulted in a reasonable ovarian response with 7 to 10 cryopreserved oocytes per patient. Noyes et al demonstrated the average length of fertility preservation treatment time to be 12 ± 0.3 days. This approach provides a significant advantage by decreasing total time for the IVF cycle, but further data are needed to determine its effectiveness compared with traditional IVF stimulation regimens.

In addition to the delay in cancer treatment, ovarian stimulation for IVF poses a theoretical risk to women with hormonally responsive cancers. Ovarian stimulation with gonadotropins for IVF often results in supraphysiologic estradiol levels of greater than 2000 pg/mL compared with normal physiologic peak estradiol levels of 200 to 350 pg/mL. The high estradiol levels sustained during IVF treatment are a particular concern in women with estrogen-receptor–positive breast cancer. In initial nonrandomized studies, stimulation protocols that include the selective estrogen receptor modulator tamoxifen or aromatase inhibitors such as letrozole administered during gonadotropin treatment decrease estradiol level production while not decreasing overall oocyte numbers. Initial reassuring data reveal that this approach has not been shown to increase short-term cancer recurrences for breast cancer patients.

Estradiol levels may be reduced after oocyte retrieval by the use of GnRH agonists instead of human chorionic gonadotropins to trigger final oocyte maturity. This has been shown to substantially reduce the risk of ovarian hyperstimulation in women undergoing IVF. This approach has been evaluated in oocyte donors undergoing oocyte vitrification and has resulted in similar numbers of oocytes retrieved in a retrospective study. There was also no significant difference in the percentage of oocytes surviving thawing, oocyte fertilization, and pregnancy rates. Further research is needed to determine if this approach will be beneficial in cancer patients undergoing oocyte or embryo banking but may further decrease any
theoretical risks of breast cancer progression or recurrence from ovarian stimulation.

Hematologic Cancer and Fertility

Hematologic malignancies such as lymphoma and leukemia are commonly diagnosed in women during their childbearing years. The 5-year survival rates for Hodgkin lymphoma and non-Hodgkin lymphoma are between 90% and 95%, and 80% and 85%, respectively. Approximately 60% of female patients diagnosed with Hodgkin disease are fertile, and after standard treatment, premature ovarian failure rates vary from less than 10% to 50%. For non-Hodgkin disease, premature ovarian failure rates vary from 5% to 15%. If the need for hematopoietic stem cell transplant is necessary, the patient should understand that the risk of premature ovarian failure is 70% to 100%. When counseling prepubertal females with lymphoma, ovarian tissue cryopreservation may currently be the only option to allow those patients access to their oocytes for future pregnancies. For those women in their fertile years, cryopreservation of oocytes is an excellent option if treatment can be delayed; if not, ovarian tissue cryopreservation or immature oocyte retrieval can be discussed.

Leukemia diagnoses vary significantly in the fertile population, with 75% of females diagnosed with acute lymphoblastic leukemia noted to be in their childbearing years, with a 64% survival rate. The incidence of acute myelogenous leukemia (AML) and chronic myelogenous leukemia (CML) in a fertile female population is between 18% and 20%, with survival rates between 23% for AML and 57% CML. The incidence of CML is significantly low in the fertile female population but is associated with a 78% survival rate. Those patients treated for AML or acute lymphoblastic leukemia have a lower risk of infertility after standard chemotherapy, and at this time, there are insufficient data regarding premature ovarian failure. When reviewing potential fertility-sparing options for leukemia patients, cryopreservation of oocytes or development of immature follicles from ovarian tissue is optimal, because of the potential risk for transfer of malignant cells back into the body with ovarian tissue cryopreservation and retransplantation.

GYNECOLOGIC CANCER AND FERTILITY

Uterine and ovarian cancers are the fourth and ninth most common tumors in the United States and are most commonly diagnosed in the postmenopausal woman. However, a portion of uterine and ovarian cancers is diagnosed in women during their childbearing years. Cervical cancer remains the most common gynecologic cancer diagnosed in fertile women, with 40% of all cases diagnosed during childbearing years. Although cervical cancer remains the only gynecologic cancer staged clinically, surgical staging and management remain a hallmark of gynecologic oncology. However, as oncofertility emerges in the gynecologic oncology field, this standard approach to staging and treatment may be modified in appropriate cases to allow for fertility-sparing surgical techniques and management options.

Candidates for fertility preservation in the face of a gynecologic malignancy must be carefully selected. The histological diagnosis and stage of cancer must be established as accurately as possible to determine if fertility preservation can even be considered. The patient must have a strong desire for future fertility, have no obvious impairments to fertility, and preferably be 43 years or younger to optimize her chance for a successful future pregnancy. Patients who opt for fertility preservation must also maintain absolute compliance with follow-up, as these patients often require varied and shorter evaluation intervals.

Uterine Cancer

Uterine cancer, with more than 49,000 new cases projected each year, is primarily a diagnosis of postmenopausal women, although 25% of cases or more are diagnosed in premenopausal women. The standard surgical approach to uterine cancer involves hysterectomy, bilateral salpingo-oophorectomy, and lymph node dissection. Fertility-sparing management has been proposed in the form of progestin therapy for young patients with a well-differentiated type I endometrial cancer and/or ovarian conservation. Progestin is thought to reverse atypical endometrial hyperplasia or low-grade carcinoma via activation of progesterone receptors, which results in decidualization and thinning of the uterine lining. In 2012, a meta-analysis evaluated the risk of recurrence of endometrial cancer after progestin therapy in patients with disease limited to the uterus. The average age of patients was 31.1 years, and the meta-analysis involved 391 subjects from 45 studies. Patients were treated with progestin therapy and underwent uterine sampling every 1 to 6 months. Patients diagnosed with endometrial hyperplasia experienced a 66% response; however, 23% ultimately had a recurrence after a complete response. Those with endometrial adenocarcinoma also noted a 48% response, with a 35% recurrence rate noted after a complete response, making...
disease persistence more common in carcinoma.\(^\text{36}\) Unfortunately, there was no definitive consensus for the progestin regimen or duration of treatment in this study or in general practice. When the fertility outcomes were investigated, a 41% and 34.8% pregnancy rate was noted in hyperplasia and endometrial carcinoma, respectively, making this management a distinct option for those endometrial hyperplasia or cancer patients who desire future fertility.\(^\text{37}\) However, in those patients who ultimately failed medical management, a hysterectomy was recommended.

The question remains as to the safety of ovarian conservation for those patients with endometrial carcinoma and those with persistent disease who may consider ovarian hyperstimulation for the purpose of oocyte retrieval and cryopreservation for fertility preservation. Studies have shown that there is a synchronous ovarian malignancy rate as high as 25% in women 25 years or younger, although this is refuted in various studies.\(^\text{38,39}\) Ovarian conservation would be contraindicated in hereditary cancer syndromes, but studies have shown that there is no change in overall survival in those who retained their ovaries at the time of hysterectomy.\(^\text{40}\) Currently, there is no substantial evidence regarding the effect of ovarian hyperstimulation on endometrial disease, and many believe these patients may undergo fertility preservation treatments.\(^\text{4}\)

**Cervical Cancer**

Cervical cancer remains the leading cause of gynecologic cancer deaths worldwide, comprising 15% of all cancers in women younger than 40 years.\(^\text{41}\) Forty-five percent of fertile patients are diagnosed with stage IBI, making the fertility-sparing procedure, a radical trachelectomy, a viable option for treatment of their disease and maintenance of future fertility.\(^\text{41}\) The radical vaginal trachelectomy has been described since 1994, with approximately 700 cases, 250 pregnancies, and 100 births reported in the literature.\(^\text{42}\) Emerging surgical techniques including laparoscopic and robotic surgery are improving perioperative outcomes for these patients, whereas neoadjuvant chemotherapy may present patients who were previously not surgical or fertility-sparing candidates.

Appropriate candidates for fertility-sparing management in the form of radical trachelectomy for cervical cancer include patients who strongly desire future fertility and have a proven diagnosis of cervical cancer. Those patients diagnosed with an unfavorable histology (clear cell, small cell neuroendocrine) and evidence of lymph node or distant metastasis are not candidates for fertility preservation, given the extremely high risk of locally or regionally advanced cancer. Those patients with a tumor of 2 cm or less and stages 1A1 with lymphovascular space invasion, 1A2, and 1B1 have been offered fertility-sparing treatment.\(^\text{41}\) Several studies show that radical vaginal trachelectomy results in equal or less perioperative morbidity than radical hysterectomy, with no difference in the recurrence rate or overall survival between the 2 techniques.\(^\text{43}\) Emerging surgical techniques including laparoscopic and robotic surgery are improving perioperative outcomes for these patients, whereas neoadjuvant chemotherapy may allow for radical trachelectomy for those patients with original cancer size of greater than 2 cm.\(^\text{41}\) Although trachelectomy is certainly not appropriate for many cervical cancer patients, it is an exciting option for those patients with early-stage disease who desire future fertility.

**Ovarian Cancer**

Ovarian cancer accounts for more than 22,000 cases annually in the United States, with 12% to 14% of those noted to be invasive ovarian cancers in women younger than 40 years.\(^\text{44}\) Primary surgery for a young woman with a pelvic mass allows for histologic diagnosis, comprehensive staging in patients with
early-stage disease, and maximum cytoreductive surgery in patients with advanced disease. Standard surgical staging for an epithelial ovarian cancer in the past has involved hysterectomy and bilateral salpingo-oophorectomy, peritoneal cytologic washings, multiple biopsies of peritoneal surfaces, omentectomy, and pelvic and para-aortic lymphadenectomy with the goal of no gross residual disease regardless of stage. When a nonepithelial (malignant germ cell, sex cord stromal, borderline epithelial) cancer is diagnosed, often a patient will be suitable to undergo a unilateral salpingo-oophorectomy with additional staging, allowing for fertility preservation. Uterine preservation may be possible in instances where bilateral salpingo-oophorectomy is necessary. The surgical approach and management of patients with both nonepithelial ovarian cancer and early-stage epithelial ovarian cancer may be modified based on their desire to retain fertility; however, fertility-sparing surgery for women of childbearing age with early-stage epithelial ovarian cancer has been strongly debated in the recent oncology literature, given the greater risk of relapse.

Nonepithelial tumors of the ovary are more commonly unilateral and early stage at the time of diagnosis. For example, 60% of germ cell tumors of the ovary are stage I, and most are unilateral. Only 10% to 15% of germ cell tumors are bilateral and usually are found to be dysgerminomas. Unilateral oophorectomy or even cystectomy with surgical staging may be considered to preserve fertility for those patients with unilateral germ cell tumors. Sex cord stromal tumors occur occasionally in premenopausal women, but the majority are noted to be unilateral tumors (95%) in postmenopausal women. Ninety percent of sex cord stromal tumors are noted to be stage I at the time of diagnosis. Borderline or low-malignant-potential tumors comprise 10% to 15% of all ovarian tumors and have a greater propensity for bilaterality, especially if there is serous histology. Approximately 50% of serous borderline ovarian tumors are bilateral, whereas only 10% to 20% of mucous borderline ovarian tumors are bilateral. When the diagnosis of a nonepithelial or borderline ovarian tumor is confirmed, studies have shown that conservative therapy in the form of unilateral salpingo-oophorectomy or even cystectomy may be appropriate.

Epithelial ovarian cancer proves a greater challenge to the concept of a conservative treatment approach, given its potential for invasiveness and metastasis. There are only a few published series that have investigated the idea of conservative surgical therapy for patients with stage I epithelial ovarian cancer, and none are conclusive. An Italian study published in 2012 looked at 240 patients with stage I epithelial ovarian cancers that were treated with fertility-sparing surgery then chemotherapy, depending on the grade and stage of cancer as well as the adequacy of staging. This study included all histological types and grades of differentiation. The median age was noted to be 32 years old, and greater than 70% were nulliparous. Twenty-six percent of those patients underwent cystectomy, whereas 74% had a unilateral salpingo-oophorectomy. The relapse rate and mortality rate for cystectomy were noted to be 17% and 6%, respectively, whereas the patients who received a unilateral salpingo-oophorectomy were noted to have a 9% and 4% relapse rate and mortality rate, respectively. However, because the number of patients treated with cystectomy is very small, it is not possible to draw definitive conclusions regarding the safety of cystectomy for epithelial ovarian cancer. This was noted to be a small retrospective study in which follow-up was only 9 years; however, an 80% pregnancy rate was noted, and 65% of patients had 1 or more children. Chemotherapy did not appear to affect fertility outcomes in this subset of patients. Although appealing, clearly further investigation is necessary before routine practice of fertility-sparing surgery in epithelial ovarian cancer.

CURRENT FERTILITY PRESERVATION OPTIONS

Embryo or oocyte cryopreservation may be offered if there is enough time for ovarian stimulation in women scheduled to undergo therapy that carries a high risk of premature ovarian failure or loss of reproductive organs. Other options such as ovarian tissue cryopreservation may be more appropriate for those patients in whom therapy is recommended to start immediately or in whom ovarian stimulation is considered unsafe, although this method of fertility preservation is still considered experimental. Establishment of ovarian reserve can help predict how vulnerable a patient may be to cancer therapies and could dictate the need for fertility preservation options. A summary of markers of ovarian reserve is provided in Table 1. It is important to note that markers of ovarian reserve have been studied primarily in the general infertility population. The sensitivity and specificity were determined based on evaluating the ovarian response to fertility medications and subsequent pregnancy in patients treated with IVF. Research in cancer patients is ongoing to determine if these markers may be predictive of ovarian function or future pregnancy after chemotherapy (Table 4).
Embryo and Oocyte Cryopreservation

The primary modalities for fertility preservation in women are oocyte or embryo cryopreservation. Embryo cryopreservation requires that a patient be willing to use a sperm donor or has an established partner with whom she agrees to create embryos. Ovarian stimulation for oocyte or embryo cryopreservation may delay cancer treatment for 2 to 5 weeks. Therefore, patients who may desire oocyte or embryo cryopreservation should be immediately referred to a reproductive endocrinologist upon the diagnosis of cancer to avoid any further potential delay in therapy. Once patients are evaluated and are appropriate for ovarian stimulation, the oocytes are retrieved, and in the event of embryo cryopreservation, ART is used to create and store embryos, which may then be transferred to the uterus at a later time. The live-birth rates after ART are generally between 40% and 50%, although live-birth rates are center-dependent. Preimplantation genetic diagnosis may be utilized in the case of hereditary cancer syndromes as a screening method for embryos before uterine transfer. Although cost varies from center to center, most embryo cryopreservation cycles cost $8000 to $12,000 per cycle, not including storage fees and the cost of a subsequent pregnancy. Many centers offer significantly discounted rates for cancer patients and participate in programs to help defray the financial burden.

Oocyte cryopreservation has just recently been established as a standard, nonexperimental option and fertility preservation. Although the first live birth from oocyte cryopreservation was reported in 1986, outcomes were not comparable to conventional embryo cryopreservation and IVF until approximately 2010. In 2012, the American Society for Reproductive Medicine released a statement proclaiming oocyte cryopreservation is no longer considered experimental. The approach to oocyte cryopreservation is very similar to that of embryo cryopreservation, in that ovarian stimulation and oocyte retrieval should be immediately referred to a reproductive endocrinologist upon the diagnosis of cancer to avoid any further potential delay in therapy. Once patients are evaluated and are appropriate for ovarian stimulation, the oocytes are retrieved, and in the event of embryo cryopreservation, ART is used to create and store embryos, which may then be transferred to the uterus at a later time. The live-birth rates after ART are generally between 40% and 50%, although live-birth rates are center-dependent. Preimplantation genetic diagnosis may be utilized in the case of hereditary cancer syndromes as a screening method for embryos before uterine transfer. Although cost varies from center to center, most embryo cryopreservation cycles cost $8000 to $12,000 per cycle, not including storage fees and the cost of a subsequent pregnancy. Many centers offer significantly discounted rates for cancer patients and participate in programs to help defray the financial burden.

Ovarian Tissue Cryopreservation

Ovarian tissue cryopreservation refers to the removal of ovarian tissue from a patient with the transplantation of cryopreserved tissue to orthotopic or heterotopic sites at a later time. This ovarian tissue may be transplanted within the peritoneum, sutured onto the natural ovary, placed subcutaneously, or even placed within the rectus sheath. Ovarian tissue transplantation can be performed in prepubertal girls and adolescents at any point in the menstrual cycle, has the potential to save large numbers of oocytes, and may allow for spontaneous pregnancy in the future without IVF or ovarian stimulation. Sixteen human live births have been reported from previously frozen, thawed tissue that was transplanted onto the native ovary, and...
both endocrine and fertility function. However, there are several concerns related to ovarian tissue cryopreservation. There is the need for an additional procedure, as well as a distinct risk of reseeding tumors after transplantation of ovarian tissue, especially in those patients with a hematologic malignancy. A small mouse study revealed that 4 of 18 leukemia patients’ xenografted ovarian tissue resulted in development of tumors. There is also a concern that primordial follicles will be lost from grafted material secondary to a delay in revascularization, premature follicular activation after grafting, or oocyte damage by cryopreservation. Despite potential concerns, ovarian tissue cryopreservation may be the only option for prepubertal females and women who cannot delay the initiation of cancer treatment or undergo ovarian stimulation.

Research is ongoing to isolate immature oocytes from ovarian tissue and mature the oocytes in vitro, referred to as in vitro maturation. The mature oocytes could then be used for IVF. At this time, in vitro maturation has been successful only in mice but may be an alternative to homologous tissue transplantation and its risk of reintroduction of malignant cells. Research efforts to establish in vitro culture methods for growing follicles are slow to develop, secondary to difficulty with tissue acquisition, lack of funding, and lack of knowledge in follicle development.

Options for Male Patients

Sperm cryopreservation is a generally minimally invasive and widely available and successful option for fertility preservation for male patients facing a malignancy diagnosis. This is recommended for all male cancer patients regardless of the risk of gonadal failure. Semen specimens will usually be produced by masturbation in those who are sexually mature, and if not possible, penile vibratory stimulation, rectal electrostimulation, or testicular or epididymal aspiration under anesthesia may be an option. After cryopreservation, stored spermatozoa may be used for IVF or intrauterine insemination depending on the amount and viability of sperm. For patients who have not yet entered puberty, the options for fertility preservation remain entirely experimental and currently include manipulation of spermatogonial stem cells.

There is also the option for sperm donation as necessary for those patients who did not have the opportunity to cryopreserve semen samples.

Additional Options

There are several methods that have been used to assist with fertility preservation in women with cancer that do not involve ovarian stimulation or cryopreservation. Ovarian transposition, transfixing the ovaries above the pelvic rim, is often utilized in the treatment of cancer that involves radiation exposure to the pelvis and may reduce the incidence of premature ovarian failure. Pelvic radiation is a standard approach to treatment in cervical, vaginal, and endometrial cancers. Transposition of the ovaries may reduce radiation exposure down to 5% to 10% of those not transposed; however, ovarian function after radiation therapy also depends on several other factors including the degree of scatter radiation, vascular compromise, the age of the patient and their baseline ovarian reserve, and whether other potentially toxic therapy was used in the treatment of the cancer.

Gonadotropin-releasing hormone agonist administration for the purpose of ovarian suppression and protection has been suggested by many physicians. The agonist, when initiated 1 month before the initiation of chemotherapy, is thought to protect the ovary by suppressing the pituitary secretion of FSH/LH, thereby decreasing the accelerated oocyte depletion after gonadotoxic therapy. This would prevent the recruitment and destruction of additional primary follicles after the elevation of FSH that is noted after initial exposure to gonadotoxic therapy. There are no large, randomized controlled trials to establish the efficacy of this method and subsequent pregnancy rates; therefore, GnRH agonist therapy should not be routinely offered to cancer patients. There are well-established sperm, oocyte, and embryo donation programs for patients facing a diagnosis of cancer in whom fertility preservation may not be an option or may not have been considered before cancer treatment. These options have tremendous potential for those patients in whom their own sperm, oocyte, or embryos are unavailable or unacceptable for use. Patients with uterine cancer who receive a hysterectomy may consider utilizing a gestational carrier.

BARRIERS TO FERTILITY PRESERVATION

Barriers to these services still exist with all of the options for potential fertility preservation. For cancer patients and even some physicians, there is a failure...
to recognize the effect of cancer treatment on fertility or the efficacy of fertility preservation options. There may also be lack of access to qualified health care providers or tertiary care centers in some areas. Furthermore, the cost itself is prohibitive to many patients, especially those without insurance or whose insurance coverage does not fund fertility preservation. Interestingly, insurance companies generally cover treatment for iatrogenic conditions that result from cancer treatment, as evidenced by the Women’s Health and Cancer Rights Act passed in 1998 to mandate breast reconstruction after a mastectomy performed for the treatment of breast cancer.55 Unfortunately, treatments for fertility preservation may fall under “elective” treatments, those that are not medically necessary, or those that are experimental. Currently, there is a lack of diagnostic criteria for such a medical condition that only potentially exists, as there are uncertain fertility outcomes after cancer treatment. Furthermore, the fact that fertility preservation is an extremely socially and ethically complex medical situation only complicates the matter of insurance coverage and availability of services.

THE GYNECOLOGISTS’ ROLE

Gynecologists are considered by most to be an extension of primary care physicians and, as primary care physicians, may provide a wide range of services to oncology patients. Primary care physicians often diagnose the original malignancy and coordinate the appropriate referrals. They provide ongoing medical care throughout cancer treatment as well as pain management and oftentimes provide counsel to the patient in regard to clinical decision making and emotional support.1 Furthermore, despite the emerging focus on fertility preservation in the face of cancer, an unintended pregnancy could be just as devastating to a patient, and fertility may not actually be compromised during the course of care. Contraception counseling, therefore, is of paramount importance before the initiation of treatment.

CONCLUSIONS

Oncofertility is an exciting new interdisciplinary field that encompasses the obstetrician gynecologist, gynecologic oncologist, reproductive endocrinologist, and primary care physician in a common goal to provide fertility preservation options for cancer patients. This involves a team-based approach to clinical care, as well as a focused approach in the basic science arenas of cancer therapeutics and ART. Cancer survivorship strives to provide cancer patients with not only excellent oncologic care, but also an acceptable quality of life after treatment is complete. Maintaining their fertility is of the upmost importance for many patients diagnosed during their childbearing years. The goal of oncofertility is to provide both physicians and patients with the knowledge and resources to make fertility an ongoing opportunity for all patients who desire a future with children.

REFERENCES


