Gynecologic Concerns in Children and Adolescents With Cancer

ABSTRACT: Advancements in radiation therapy, chemotherapy, surgery, and multimodal treatment have dramatically improved childhood cancer survival. However, cancer and its treatment may have immediate or delayed adverse effects on reproductive health. Gynecologists should be prepared to manage gynecologic concerns in young cancer patients and survivors before, during, and after their treatment. Gynecologists may be consulted regarding pubertal concerns; heavy menstrual bleeding and anemia; sexuality; contraception; ovarian function, including fertility preservation; and breast and cervical cancer screening. The science of fertility preservation is a rapidly evolving field; therefore, a referral to a reproductive endocrinologist is recommended to explore the full range of available options.

The diagnosis of cancer during childhood, adolescence, and young adulthood is rare, with the incidence of invasive cancer at any site for females younger than 20 years in the United States at 20 cases per 100,000 individuals per year (1). Advancements in radiation therapy, chemotherapy, surgery, and multimodal treatment have dramatically improved childhood cancer survival, with the 5-year survival rate reaching almost 80% (2). Cancer and its treatment may have immediate or delayed adverse effects on reproductive health. Gynecologists may be consulted regarding pubertal concerns, menstrual irregularities, sexuality, contraception, and ovarian function, including fertility preservation during and after cancer treatment. Although advancements in cancer therapy have dramatically improved childhood cancer survival, gynecologists should be aware of the increased risk of adverse reproductive health effects from each type of therapy. The purpose of this document is to update gynecologists regarding the adverse effects of specific cancer treatments and the management of gynecologic issues in young cancer patients and survivors.

Cancer Therapy and Toxicity

Radiation

Pelvic irradiation results in ovarian follicle loss, impaired follicular maturation, and cortical and capsular damage (3). Determinants of ovarian dysfunction after radiation treatment include dosage, age, and pubertal development at the time of exposure; the extent of the radiation treatment field; and the concomitant use of chemotherapeutic agents. Ovarian tissue demonstrates a dual sensitivity to radiation therapy and chemotherapy, with reduced future fertility from gonadal failure noted in women who receive more than 5 Gy in one dose (Table 1) (4). For a frame of reference, a diagnostic X-ray delivers between 0.3 mGy and 3 mGy of radiation. Radiation oncologists, therefore, have minimized the toxicity of pelvic irradiation by dividing the dose into multiple smaller doses (termed “fractions”). The dose of fractionated radiation therapy at which ovarian failure occurs immediately after treatment in 97.5% of females (also known as the “effective sterilizing dose”) is 20.3 Gy (divided into 1.5–2.0 Gy fractions) at birth and decreases to 16.5 Gy at age 20 years (5). Primary ovarian insufficiency caused by radiation can lead to infertility and decreased libido in adolescents and young women. In addition to ovarian follicle loss, pelvic irradiation may have site-specific effects on the uterus after 14–30 Gy, which may lead to future adverse pregnancy outcomes, including spontaneous miscarriage, preterm birth, and low birth weight (6). Other pelvic organs have a higher...
tolerance to radiation therapy, with the vaginal epithe-
lium and cervix tolerating doses of 90–100 Gy before
fibrosis, dyspareunia, or fistula develop.

Cranial
Endocrine dysfunction is common in survivors of child-
hood brain tumors as a consequence of either the
tumor or treatment (7). Disruption of the hypothalamic–
pituitary–ovarian axis is a well-established potential
complication found in survivors of central nervous sys-
tem tumors that can lead to amenorrhea and infertility.
Cranial irradiation also may induce precocious puberty
by causing cortical disinhibition of the hypothalamus
(8). Additional endocrine effects that may contribute
to menstrual dysregulation in survivors of childhood
brain tumors who receive radiation therapy directed at
the hypothalamus include growth hormone deficiency,
hypothyroidism, and adrenocorticotropic hormone defi-
ciency (7, 9).

Chemotherapy
The effect of chemotherapeutic drugs on ovarian func-
tion depends on the patient’s age at the time of treat-
ment, the type and dose of the chemotherapeutic agent,
and the number of chemotherapy cycles. Alkylating
agents are associated with the most significant risk of
gonadal dysfunction (Box 1). The risk of gonad toxicity
is directly proportional to the age and pubertal status of
the patient at the time of exposure. That is, the older the
patient is at the time of treatment, the higher her risk
of early ovarian failure. Ovarian insufficiency can be
transient or permanent. Depending on pubertal matura-
tion level, peripubertal exposure can result in delayed or
arrested puberty. Postpubertal exposure may lead to oli-
gomenorrhea, amenorrhea, or compromised fertility (10).

Surgery
Surgical resection of the vagina, uterus, ovaries, or fallo-
pian tubes to treat malignancy will obviously affect fertil-
ity. Debulking for abdominal and pelvic tumors, such as
Wilms tumor or rhabdomyosarcoma, also may lead to
adhesions and infertility, pelvic pain, sexual dysfunction,
and fistula formation. In some cases, fertility-sparing
surgery can be performed; for example, leaving in the
uterus when both ovaries are affected to enable patients to
undergo donor-egg pregnancies in the future.

Specific Gynecologic Concerns
Gynecologists should be prepared to manage gynecologic
concerns in young cancer patients and survivors before,
during, and after their treatment. Gynecologists may be
consulted regarding pubertal concerns; heavy menstrual
bleeding and anemia; sexuality; contraception; ovarian
function, including fertility preservation; and breast and
cervical cancer screening.

Pubertal Development
The patient’s age at the time of treatment and the type
of treatments recommended for childhood cancer may
alter pubertal development. The effects of cancer treat-
ments on pubertal development range from precocious
puberty to delayed or arrested puberty to primary ovarian
insufficiency. Central nervous system tumors located in
the hypothalamic–pituitary regions may involve surgical

Table 1. Cytotoxic Effect of Ovarian Irradiation

<table>
<thead>
<tr>
<th>Minimum Ovarian Radiation Dose–Total Dosage (Gy)</th>
<th>Effect</th>
</tr>
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<tbody>
<tr>
<td>0.6</td>
<td>None</td>
</tr>
<tr>
<td>1.5</td>
<td>None in females younger than 40 years</td>
</tr>
<tr>
<td>2.5–5.0</td>
<td>Permanent ovarian failure in 60% of females aged 15–40 years</td>
</tr>
<tr>
<td></td>
<td>May cause transient amenorrhea</td>
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</tbody>
</table>

Data from Friedman DL. The ovary. In: Schwartz CL, Hobbie WL, Constance LS, Ruccione KS, editors. Survivors of childhood and adolescent cancer: a multidisci-

Box 1. Chemotherapeutic Agents That Increase the Risk of Ovarian Dysfunction

Alkylating agents
- Busulfan
- Carmustine
- Chlorambucil
- Cyclophosphamide
- Ifosfamide
- Lomustine
- Mechlorethamine
- Melphalan
- Procarbazine
- Thiopeta

Nonclassical alkylators
- Dacarbazine
- Temozolomide

Heavy metals
- Carboplatin
- Cisplatin

resection and radiation therapy, leading to precocious puberty in some cases and delayed puberty in others. Precocious puberty occurs most frequently in children who were younger at the age of tumor diagnosis (7). Patients who receive more than 24 Gy of cranial irradiation or who are 4 years or younger at radiation therapy onset are reported to be at increased risk of early puberty, although early pubertal effects have been reported at doses as low as 18–24 Gy (11).

Girls who are exposed to gonadal toxic therapy may experience a delay or arrest of pubertal development. Hormonal treatment for induction of puberty and progression of sexual maturation is appropriate for girls with arrested pubertal development and should be addressed in collaboration with a pediatric endocrinologist. Hormonal replacement may be indicated to improve long-term quality of life for girls with ovarian failure who have completed the pubertal process; to date, there are few data on hormonal therapy treatment regimens for the adolescent population (12). The completion of puberty is the appropriate timing for intervention; otherwise there is a risk of premature closure of the epiphysis.

Heavy Menstrual Bleeding and Anemia
Cancer and its treatments place young women at risk of heavy menstrual bleeding and anemia. Even normal menstrual blood loss may be associated with adverse outcomes in women who are already anemic. There are several options for menstrual management, which are discussed in Committee Opinion No. 606, Options for Prevention and Management of Heavy Menstrual Bleeding in Adolescent Patients Undergoing Cancer Treatment (13). Each treatment carries potential risks, benefits, and secondary benefits. Ideally, therapy for menstrual suppression should be initiated before the onset of cancer treatment after thorough consultation among the young woman, her oncology team, and her gynecologist.

Contraception
Pregnancy during cancer treatment may result in a decision to delay treatment or terminate the pregnancy (14). Furthermore, first-trimester exposure to chemotherapy and radiation is associated with an increased risk of congenital malformations (15). Sexually active young women should be thoroughly educated about the risks of becoming pregnant during cancer treatment and strongly encouraged to use effective contraception. Medical eligibility for contraceptive use (www.cdc.gov/mmwr/pdf/rr/rr5904.pdf) should be considered carefully because each young woman may have special considerations during and after cancer treatment (16, 17). Risks and benefits of contraceptives should be considered along with possible therapeutic effects, such as induced amenorrhea. For more information about menstrual regulation, see Committee Opinion No. 606, Options for Prevention and Management of Heavy Menstrual Bleeding in Adolescent Patients Undergoing Cancer Treatment (13).

Acute, Transient, and Delayed Primary Ovarian Insufficiency
Some cancer survivors may experience acute ovarian failure, defined as loss of ovarian function within 5 years of a diagnosis of cancer. In a study of 3,390 childhood cancer survivors, 6.3% experienced acute ovarian failure (18). Risk factors for acute ovarian failure were older age at diagnosis, Hodgkin lymphoma, increasing ovarian radiation doses, and increasing exposure to alkylating agents. In another study of 2,819 childhood cancer survivors, the risk of nonsurgical premature ovarian failure before age 40 years was 8% compared with 0.8% in sibling controls (19). Primary ovarian insufficiency puts women at risk of psychosexual dysfunction, infertility, and osteoporosis. Most girls with primary ovarian insufficiency are candidates for long-term hormonal treatment at replacement doses to reduce symptoms of estrogen deficiency and long-term risks of fractures and ischemic heart disease (20). See Committee Opinion Number 605, Primary Ovarian Insufficiency in Adolescents and Young Women for more information on diagnosis and evaluation (21).

Breast and Cervical Cancer Screening
A recent systematic review showed a substantially increased risk of breast cancer in women previously treated with chest irradiation, most of whom were treated for Hodgkin lymphoma, with a cumulative incidence of 13–20% by age 40–45 years (22). Women and girls who received thoracic irradiation between age 10 years and 30 years have an increased risk of cancer and should be advised to receive the following screening regimen beginning 8–10 years after they received treatment or at age 25 years, whichever occurs last: annual mammography, annual breast magnetic resonance imaging (MRI), and screening clinical breast examination every 6–12 months (23, 24). It is important to note that screening mammography in women younger than 40 years has reduced sensitivity compared with breast MRI, so these recommendations will likely evolve as the role of breast MRI becomes more established.

Cervical cytology screening guidelines remain unchanged from the general population unless the cancer survivor remains immunosuppressed. No studies or major society recommendations exist to guide cervical cytology management in girls and young women who are immunocompromised because of cancer treatments. However, the Centers for Disease Control and Prevention recommends that cervical cytology screening for women who are immunocompromised because of human immunodeficiency virus (HIV) infection should be initiated at the age when the diagnosis of HIV was established, even if younger than 21 years (25). There is not enough evidence to determine whether or not girls or young women who are immunocompromised because of other causes should undergo cervical cytology screening at the onset of sexual activity or wait until age 21 years.
Future Fertility and Fertility Preservation

In the largest study of childhood cancer survivors, the relative risk of pregnancy among adult cancer survivors who were not surgically sterilized was 0.81 (95% confidence interval, 0.73–0.90) compared with their sibling cohort (4). Reduced fertility was associated with a hypothalamic or pituitary radiation dose greater than or equal to 30 Gy, or an ovarian–uterine radiation dose greater than 5 Gy, or increased use of alkylating agents (4). See Box 1 for a list of alkylating agents.

When compared with gonadotropin levels, antimüllerian hormone level is the optimal screening tool for assessing ovarian reserve in survivors of childhood cancer. A study of 53 females demonstrated the utility of antimüllerian hormone level as a screening tool for assessing ovarian reserve in female childhood cancer survivors, although the authors noted the limitations of its cross-sectional study design (26). In young girls and women who might be at risk of infertility with cancer treatment, potential options for fertility preservation should be discussed before treatment. For women who will be treated with pelvic irradiation, oophoropexy to move the gonads away from the radiation field may have a protective effect (27). If there is adequate time and a safe method for ovarian stimulation before cancer treatments, cryopreservation of either oocytes or embryos also may be offered (28). Cryopreservation of ovarian tissue with autologous transplantation or maturation of primordial follicles has been successfully described (29). The science of fertility preservation is a rapidly evolving field; therefore, a referral to a reproductive endocrinologist is recommended to explore the full range of available options. Additionally, there are ethical issues that involve minors and their ability to give voluntary informed consent, assent, or refusal for procedures or experimental treatments related to fertility preservation.

For young women who have completed sexual development, gonadotropin-releasing hormone agonists, such as leuprolide acetate, have been used to induce ovarian quiescence in an effort to preserve ovarian function and fertility after cytotoxic treatment. Results of this method have been mixed, but a recent meta-analysis of nine observational studies that involved 366 women who received leuprolide acetate during cyclophosphamide treatment showed a slight increase in ovarian function compared with untreated women (30). At this time, the evidence is not strong enough to recommend this therapy, but multiple prospective randomized trials are underway.

Pregnancy Outcomes

A history of cancer and cancer treatment may have an effect on the outcome of future pregnancies. Childhood cancer survivors who maintain fertility should be counseled on the health risks to offspring in addition to potential pregnancy-related complications. Investigators from the Childhood Cancer Survivors Study found that compared with sibling-matched controls, childhood cancer survivors were less likely to become pregnant (31). Offspring born to survivors with germline cancer predisposing mutations had a greater risk of cancer (32). Several studies have demonstrated that chemotherapy does not adversely affect fetal growth and development or uterine function; however, cardiac decompensation may occur in pregnant women previously treated with anthracycline antibiotics such as doxorubicin or daunorubicin (31). In long-term follow-up studies of the pregnancies of childhood cancer survivors who received radiation therapy, the risk of congenital malformations, genetic disorders, and cancer was the same as it was for their sibling controls; however, the risk of premature birth and low birth weight was increased compared with sibling controls when specifically exposed to pelvic irradiation (10). Other adverse pregnancy outcomes such as fetal malposition, abnormal placenta, maternal pregnancy induced hypertensive disorders, postpartum hemorrhage, and uterine rupture also have been reported (33–35).

Conclusions

Gynecologists should be aware that childhood cancer treatments may have significant effects on ovarian function and reproductive health. Antimüllerian hormone level is the preferred biochemical marker to monitor ovarian reserve after cancer treatments. Radiation therapy, chemotherapy, and surgical intervention necessary to treat childhood cancer may adversely affect pubertal development, menstrual patterns, psychosexual functioning, fertility, and future pregnancy outcomes. Special consideration should be given to optimize fertility potential.

References


Committee Opinion No. 607