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Review Article

Oncofertility for women with gynecologic malignancies

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HIGHLIGHTS

- Oncofertility addresses fertility and reproductive health needs for cancer patients.
- In women with new diagnoses of gynecologic cancers, strategies for fertility preservation exist.
- Patients should be informed about assisted reproductive technology options.

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ABSTRACT

The emerging field of oncofertility addresses fertility and the reproductive health needs for cancer patients, a key topic in cancer survivorship. Given that the standard treatment for gynecologic malignancies involves removal of reproductive organs, pelvic radiation, or chemotherapy, the effect of such treatment on fertility and options for fertility preservation are even more relevant than for other malignancies.

In young women with new diagnoses of cervical, endometrial, or ovarian cancers, viable strategies for fertility preservation without compromising oncological outcome exist and should be considered. We present here a comprehensive review of the literature as it pertains to gynecologic malignancies on 1) the effects of radiation and chemotherapy on fertility, 2) fertility-sparing surgeries and the role of assisted reproductive technology, and 3) fertility preservation in adolescent girls and women with BRCA germline mutations.

Contents

1. Introduction

Almost 100,000 new cases of gynecologic malignancies are diagnosed each year and 15–20% of these cases are in women under the age of 40 [1]. Per the 2010 Surveillance, Epidemiology and End Results

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(SEER) statistics, 8% of endometrial cancers, 12% of ovarian cancers and 40% of cervical cancers are diagnosed during reproductive years. Standard treatment for these cancers may include hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, and adjuvant therapy in the form of pelvic radiation or chemotherapy – all of which have a detrimental effect on female reproductive potential. The emerging field of oncofertility addresses fertility and the reproductive health needs for cancer patients, a key topic in cancer survivorship [2]. In 2006, the American Society of Clinical Oncology officially recommended that patients to be educated about the effect of cancer treatment on fertility and fertility treatment options [3].

In this review, we will focus on gynecologic malignancies and first discuss the effect of pelvic radiation and chemotherapy on fertility and reproductive outcomes. Next, we will focus on fertility preservation strategies for cervical cancer, endometrial cancer, and ovarian cancer. We will review the options provided by assisted reproductive technology. Last, we will address two specific populations, which require special attention for fertility preservation – girls and adolescents, and women with BRCA germline mutations.

2. Radiation

Abdominal and pelvic radiation often used in the treatment of gynecologic malignancies may lead to accelerated *oocyte atresia*, causing early ovarian aging, insufficiency and dysfunction. This is thought to occur in a dose-response relationship as oocytes are highly sensitive to ionizing radiation. The impact may vary during the stage of the oocyte, as primordial oocytes more resistant to the effect of radiation than maturing follicles [4]. Some authors suggest that total-body irradiation and pelvic or whole-abdomen radiation >6 Gy in adult women pose a high risk for amenorrhea and ovarian failure, whereas ovaries of pre-and post-pubescent girls can likely tolerate a higher dose of radiation [5]. Through mathematical modeling, Wallace et al. proposed that the effective sterilizing dose needed to cause immediate ovarian failure is smaller with increasing age of treatment [6] – 20.3 Gy at birth, 16.5 Gy at age 20 and 14.3 Gy at age 30. This model may have prognostic value and provide additional information to counsel patients about their reproductive potential following treatment; however, the size of the radiation field, the number and magnitude of fractions, and the cumulative dose must also be taken into account. Furthermore, the specific amount of radiation that ovaries are exposed to is challenging to determine due to scatter radiation and the difficulty in identifying the exact location of ovaries on imaging. In the Childhood Cancer Survivor Study (CCCS), a large retrospective cohort study, ovarian failure was associated with older age at the time of diagnosis (Odds Ratio (OR) 1.8, $p < 0.001$) and treatment with abdominal or pelvic radiation (OR 25.4, $p < 0.001$), especially with doses ≥10 Gy [7].

In addition to the gonadotoxic effect on ovaries, *uterine exposure* to radiation has been associated with adverse pregnancy outcomes. Following pelvic radiation, uterine volumes are smaller and median cervical length shortened as compared to age-matched controls on magnetic resonance imaging (MRI) [8]. Additionally, myometrial and endometrial atrophy, fibrosis and tissue ischemia can be seen [9]. The extent of injury to the uterus depends on several factors: dose of radiation, age of the patient, and site of treatment, with most of the data derived from younger women treated with radiation therapy in childhood [10,11]. These changes may interfere with embryo implantation and lead to pregnancy-related complications including miscarriage, preterm delivery and low birth weight of offspring [12,13]. In one of the largest cohort studies to date of childhood cancer survivors, Signorello et al. demonstrated that compared to children of survivors who did not receive radiotherapy, offspring of women treated with high dose pelvic radiation (>5 Gy) were at an elevated risk of preterm delivery (OR 3.5, 95% Confidence Interval (CI) 1.5–8.0, $p = 0.03$), low birth weight (OR 6.8, 95% CI 2.1–22.0, $p = 0.001$), and being small for gestational age (OR 4.0, 95% CI 1.6–9.8, $p = 0.003$) [12].

3. Chemotherapy

Adjuvant chemotherapy is often used in the treatment of gynecologic malignancies. Chemotherapeutic agents have varying degrees of gonadotoxicity and the risk of ovarian failure depends on mechanism of action, dose and length of treatment, and age of the patient at the time of treatment. Younger patients have a more robust ovarian reserve, which translates into a lower risk of chemotherapy-induced amenorrhea. While not an exhaustive list, commonly used regimens in gynecologic malignancies include the use of alkylating agents (cyclophosphamide and ifosfamide), platinums (cisplatin and carboplatin), taxanes (paclitaxel), anthracyclines (doxorubicin), and antimetabolites (gemcitabine and 5-fluorouracil). Table 1 summarizes the gonadoxicity risk of commonly used chemotherapy agents.

Alkylating agents are associated with the highest risk for infertility and ovarian insufficiency, due to damage to the oocytes via single-stranded DNA breaks [5]. Alkylating agents are not cell-cycle specific and do not require cell proliferation for cytotoxic action, targeting primordial follicles and resting oocytes [14]. In a premenopausal breast cancer population treated with cyclophosphamide, methotrexate and 5-fluorouracil, chemotherapy-induced amenorrhea has been reported at 61% in women <40 years of age, and 95% in women ≥40 [15].

Platinum agents, taxanes, and anthracyclines are in an intermediate risk group for gonadotoxicity [16]. Cisplatin and carboplatin, both commonly used in gynecologic malignancy treatment regimens, cause DNA damage through formation of inter- and intra-strand crosslinks that cause changes in DNA conformation and affect replication. Paclitaxel, often used in combination with the platinum-based agents, inhibits microtubule formation and spindle function and has been found to damage mature oocytes in animal studies and affect short term-reproductive potential [17]. In combination with cisplatin, treatment with paclitaxel in young female rats was found to cause significantly lower numbers of primordial follicles, as compared with controls [18]. Doxorubicin, an anthracycline agent, works via intercalation of DNA and inhibition of replication and transcription. While previously thought to be only weakly gonadotoxic, recent studies have demonstrated that doxorubicin causes apoptotic damage to both oocytes and granulosa cells in an in vivo xenograft and in vitro models of the human ovary [19]. Rates of amenorrhea following treatment with anthracyclines are variable in the literature. Regimens that include doxorubicin have lower incidences of amenorrhea following treatment due to lower cumulative alkylating agent dose, and are reported at rates of 34–59% [20,21], again extrapolated from data in premenopausal breast cancer patients.

Drugs in the anti-metabolite category, such as gemcitabine and 5-fluorouracil, are generally thought to be less gonadotoxic than alkylating agents [22]. The use of methotrexate and 5-fluorouracil in breast cancer treatment regimens has not been associated with higher rates of amenorrhea [23]. Translational studies in rats have demonstrate

Table 1
Gonadotoxicity of commonly used chemotherapy agents.

Chemotherapeutic agent	Risk of gonadotoxicity	Mechanism of action
Alkylating agents Cyclophosphamide Ifosfamide	High	Induces single-stranded DNA breaks, targets primordial follicles and resting oocytes
Platinums Cisplatin Carboplatin	Intermediate	Induces chromosomal damage and DNA cross-links
Taxanes Paclitaxel	Intermediate	Inhibits microtubule formation and spindle function
Anthracyclines Doxorubicin	Intermediate	Inhibits DNA replication and transcription
Antimetabolites Gemcitabine 5-Fluorouracil	Low	Acts primarily on cells synthesizing DNA

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