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Ovarian effects of radiation and cytotoxic chemotherapy damage

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A B S T R A C T

Oncologic therapy including chemotherapy and radiation can have a significant impact on ovarian function for young women and girls. Poor health outcomes and loss of fertility are major considerations. The effect of radiation and chemotherapy on ovarian function varies depending on patient age, therapy type and dosage, and cancer type. Surgical and medical interventions are available to reduce the morbidity of premature ovarian failure associated with cancer-directed therapy. Fertility preservation is an important consideration, and several options are available for it; therefore, early consultation with a reproductive or oncofertility specialist is an essential part of oncologic care in young women or girls. This chapter will focus on the effects of radiation and chemotherapy on ovarian function and strategies to improve the reproductive care in women with cancer.

Introduction

It is estimated that more than 1.6 million new cancer cases were diagnosed in the United States in 2017. Approximately 4% of these cases, more than 67,500, were diagnosed in patients under the age of 35 years [1]. After completion of cancer therapy, young cancer survivors face both short- and long-term effects. For young women, oncologic therapies may have a significant impact on ovarian function. For example, the Childhood Cancer Survivor Study reported an incidence of premature ovarian failure

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in ~8% cancer survivors compared to <1% in the sibling group [2]. Chemaitilly and colleagues reported a prevalence of 10.9% of premature ovarian insufficiency in childhood cancer survivors [3]. Furthermore, ovarian resilience against oncologic therapies is diminished as age increases beyond childhood [4,5].

Although the benefits of oncologic therapy include sustained remission and cure, the sequelae of premature loss of ovarian function can undoubtedly have undesirable effects for a woman. In addition to the loss of fertility, decreased ovarian function may lead to premature onset of menopause, which is associated with hot flushes, loss of bone mineral density, and negative cardiac outcomes. The overall impact of diminished ovarian function or ovarian failure may lead to a poor quality of life and even premature death [6–10].

Therefore, a significant number of women will require counseling and education on ovarian and reproductive health. Clinicians must be prepared to have discussions regarding the effects of therapies on ovarian function as well as potential treatment or management options. This review will discuss the effect of radiation and chemotherapy on ovarian function and opportunities for improvement.

Normal ovarian function

The functional unit of an ovary is the follicle, which comprises the oocyte as well as the surrounding granulosa and theca cells. The cells that make up the follicle highlight the principle functions of the ovary, the production of hormones, and fertility through the maturation and release of oocytes. Women are born with a finite number of oocytes and ovarian functional reserve. After peaking at 6–7 million germ cells at 20 weeks of gestation, the number of oocytes declines to approximately 2 million at birth. Further decline is noted throughout adolescence and adulthood with an estimated 200,000 oocytes at puberty; this decline continues throughout the reproductive period. This rapid decline throughout a woman's life is attributed to apoptosis without the development of new oocytes [11,12].

Puberty is defined as the time of transition from sexual immaturity to sexual maturity and is associated with immense physical development and change. These changes include bone growth and mineralization, a growth spurt, development of secondary sexual characteristics (breast development, pubic hair development), and cardiovascular and neurologic changes. In fact, approximately 17–18% of adult growth occurs during puberty, and approximately half of the total calcium in the body is deposited within the bones during this period [13,14]. Additionally, menarche and reproductive potential are a part of normal puberty.

After menarche, normal mature ovaries continue to produce hormones like estradiol and progesterone and continue to release an oocyte monthly. This occurs until menopause, at which time the ovarian function is diminished and only an estimated 400 oocytes are remaining. Even though menopause is defined as cessation of menstrual cycles, the ovaries likely continue to play a critical role in a woman's health. In 2005, Parker et al. reported a Markov decision analytic model by analyzing several cohorts of data to assess the risks and benefits of elective oophorectomy in women aged from 40 to 80 years. The model showed that elective oophorectomy before the age of 65 years was associated with decreased overall life expectancy and increased death due to coronary artery disease. Additionally, the model concluded that elective oophorectomy before the age of 55 years increased the risk of a woman dying due to coronary artery disease by the age of 80 years by an excess of 8.5% [15]. The data suggest that even after menopause, the ovaries likely continue to have substantial health benefits.

Pathophysiology of oncologic therapy and ovarian function

There are several factors that can lead to diminished ovarian function, including chromosomal defects, autoimmune disorders, smoking, and infection [16–19]. Understandably, oncologic therapies, particularly chemotherapy and radiation, are leading causes of ovarian dysfunction. Although radiation therapy and some chemotherapy agents may result in unrecoverable damage, after administration of certain cytotoxic therapies, ovarian function may resume allowing for fertility and the continued hormonal benefits [20,21].

The repercussions of loss of ovarian function occur in both acute and late phases. The acute loss of ovarian function leads to menopausal symptoms. In addition to hot flushes, women may experience mood swings, vaginal dryness/atrophy, irregular or lack of menses, etc. The late ramifications include inability for pubertal development, decreased bone density (osteopenia/osteoporosis), cardiovascular disease, and loss of fertility. Furthermore, depression and decreased quality of life have been reported in both phases of ovarian failure [6–10]. Although the symptoms of ovarian failure may be mitigated with the use of hormonal replacement, certain circumstances such as hormone-sensitive cancers or medical contraindications may not be amenable to this option.

The discussion of the effects of oncologic therapy on ovarian function cannot be complete without mentioning the loss of ovarian function due to other causes related to the treatment of cancers. This may include central causes such as brain irradiation, pituitary surgery, or ovarian surgery (oophorectomy) resulting in surgical menopause. As these are outside the scope of this review, we will focus on the primary effects of radiation and chemotherapy on the ovaries.

Predicting the effect of chemotherapy and radiation on the ovaries

Several variables such as age, therapy type and dose, and cancer site should be considered when attempting to predict the effects of therapy on ovarian function. Early discussion with the patient regarding the impact of therapy on reproductive and overall health must be discussed. Table 1 highlights counseling considerations in women and girls planning to undergo oncologic therapy.

Chemotherapy

As most cytotoxic therapies are dependent on the cell cycle, the ovaries tend to be more resilient to cytotoxic therapy than to radiation therapy. In previous reports [25,26], the number of total follicles did not seem to be significantly impacted by chemotherapy, thus reflecting the relative resistance of oocytes to the therapy. However, there did appear to be impaired follicular maturation likely from the cellular death of the stromal cells, which are mitotically active. This latter observation explains the high levels of transient amenorrhea seen with chemotherapy administration with subsequent resumption of normal menses [20,27,28].

Not surprisingly, there is heterogeneity between the effects on ovarian function and different chemotherapy types. Alkylating chemotherapeutics are most likely to cause ovarian failure. Drugs such as cyclophosphamide, which is one of the most reported inciting agents for ovarian failure, are not reliant on cell cycle or cellular division and have a global impact on ovarian function in females of any age. By contrast, antimetabolite chemotherapeutics have a greater impact on cells undergoing division and thus have a minimal impact on the nonmitotically active oocytes [29]. When administering multiagent chemotherapy regimens, ovarian toxicity is usually determined by the most gonadotoxic agent in the regimen. Unfortunately, for several drugs, the effect on the ovaries has not been clearly elucidated or is unknown. Table 2 provides a list of common chemotherapeutic agents and their suspected ovarian effects.

Table 1
Counseling consideration for women and girls planning to undergo oncologic therapy.

Counseling considerations for women and girls planning to undergo oncologic therapy	1. Patient age 2. Chemotherapy agent/regimen ovarian toxicity 3. Dosage of therapy (radiation or chemotherapy) 4. Type and location of malignancy 5. Fertility desires 6. AMH level 7. Risk for ovarian involvement, estrogen-sensitive tumors
Fertility counseling considerations	1. Patient age (if minor, engage guardians, consider patient autonomy and local legal considerations) 2. Partner available for insemination or willingness to use sperm bank 3. Urgency to begin oncologic therapy (induction time for ovarian stimulation) 4. Prognosis 5. Cost

Table 2
Ovarian failure risk with oncologic therapies [2,25,29,31,32,37,39,43,91].

Risk for ovarian failure	Chemotherapeutic agents	Radiation considerations
High	Cyclophosphamide	Whole abdomen or pelvic radiation
	Busulfan	
	Ifosfamide	>15 Gy prepubertal
	Procarbazine	>10 Gy postpubertal
	Melphalan	Total body radiation doses
	Chlorambucil	Cranial/Brain radiation
	Carmustine	
Moderate	Doxorubicin	Whole abdominal or pelvic RT
	Vinblastine	10 to 15 Gy in prepubertal girls
	Cytosine arabinoside	
	Cisplatin	5 to <10 Gy in postpubertal girls
	Etoposide	
Low	Methotrexate	
	5-Fluorouracil	
	Vincristine	
	Mitomycin	
Uncertain	Trastuzumab	
	Bevacizumab	
	Cetuximab	
	Erlotinib	
	Imatinib	
	Paclitaxel	
	Bleomycin	
	Oxaliplatin	

In addition to the specific agent, age and dose also impact the effect of chemotherapy on the ovaries. Younger age seems to be protective of ovarian function, for instance, patients with breast cancer who are younger have lower rates of amenorrhea when treated with cyclophosphamide versus older women across several studies [30–35]. Moreover, the rate of amenorrhea in older women occurs at a short interval after chemotherapy initiation and is more likely to be irreversible [30,35–37]. Similar observations were reported for different chemotherapy regimens including those with doxorubicin among others [38,39]. Chemotherapy dose may also have an impact on ovarian function; however, the results have been variable and are often difficult to interpret, as most studies have evaluated different chemotherapy regimens [40–42]. With this in mind, caution should be exercised when counseling regarding the impact of specific chemotherapy agents on ovarian function.

Finally, the type of cancer treated may have an impact on ovarian function as well. Sklar [2] reported on a large group of early menopause women who survived childhood cancer and found a higher risk of premature ovarian failure among women treated for Hodgkin lymphoma than those treated for other cancers. De Bruin et al. [43] also examined this population evaluating treatment-related risk factors for premature menopause. They found that chemotherapy was associated with a 12.3-fold increase in risk for premature menopause compared to radiotherapy alone (supradiaphragmatic radiation or with radiation to para-aortic lymph nodes and/or spleen alone). Additionally, treatments with alkylating agents and cyclophosphamide were strongly associated with ovarian failure. The work highlights that even within a certain cancer type, there can be significant differences and counseling must include multiple variables.

In efforts to predict the impact of chemotherapy exposure on ovarian function, researchers have evaluated the role of anti-Mullerian hormone (AMH). The serologic AMH level has been shown to decrease with chemotherapy administration. Furthermore, AMH levels remain low in women who do not have resumption of normal ovarian function [44,45]. Data have also shown that women who have a higher AMH level before and after the administration of chemotherapy are more likely to have continued ovarian function [46]. Therefore, AMH levels may be a useful tool for counseling women regarding their ovarian reserve and helping patients and physicians to strategize options for symptom management and fertility planning.

Radiation

The effect of radiation on ovarian function is not dependent on cell cycle or rapidly dividing cells. Therefore, unlike cytotoxic therapies, the effect of radiation on the ovaries is much more predictable. Oocytes and ovarian stroma are exquisitely sensitive to radiation therapy. Wallace and colleagues [47] using a mathematical equation calculated the LD50, defined as the dose of radiation required to destroy 50% of the oocytes, to be less than 2 Gy. In a follow-up study, the same authors calculated the dose of radiation that would result in ovarian failure in 97.5% of patients: at birth (20.3 Gy), 10 years of age (18.4 Gy), 20 years of age (16.5 Gy), and 30 years of age (14.3 Gy) [5]. We can conclude that all therapeutic radiation treatments to the pelvic area will likely cause irreversible ovarian damage. Table 2 includes radiation considerations for ovarian function.

Options to prevent or reduce premature ovarian failure

As the impact of oncologic therapies has been well established, opportunities to minimize or prevent ovarian dysfunction are an area of significant interest. The longstanding benefits of ovarian function are related to the production of hormones as well as the preservation of fertility. Efforts to protect ovarian function are continually being evaluated, and maintaining hormonal function or fertility should be considered and offered to eligible candidates before the initiation of therapy. Of note, women with cancers that have a higher predisposition to ovarian metastases, or those with estrogen-sensitive tumors, should proceed with caution when discussing ovarian transposition or other ovarian preservation techniques [48]. Women should also be aware that the success of these interventions depends on multiple factors including the specific treatments, doses and number of treatments, and the time of therapy. This section will review several of the more common methods that have been described or are being further evaluated for the preservation of ovarian function in the appropriate candidates (Table 3).

Women undergoing chemotherapy

Chemotherapy may induce ischemic changes and fibrosis of ovarian tissue resulting in premature ovarian insufficiency or ovarian dysfunction [49]. In addition to patient factors, the extent of damage is often dependent on the dose and the type of chemotherapy agent(s), as specific cytotoxic agents may be more gonadotoxic than others (Table 2).

Surgical techniques are not expected to salvage ovarian function in women undergoing systemic therapy but may play a significant role in fertility preservation. Therefore, efforts to prevent premature ovarian insufficiency have targeted methods to slow the depletion of ovarian follicles by preventing follicular recruitment (or promoting ovarian suppression) as well as reducing blood flow to the ovary. On the basis of this concept, most studies in this area have focused on gonadotropin-releasing hormone agonists (GnRHa) [49–52]. However, studies have been limited by varying doses and duration of the GnRHa administration, lack of standardization of chemotherapy regimens evaluated, and lack of control for other factors including baseline ovarian function and age [49,50,52–54].

Table 3
Fertility and ovarian failure prevention for prepubertal and postpubertal women and girls.

	Ovarian failure prevention	Fertility preservation
Prepubertal	Ovarian transposition Ovarian tissue cryopreservation[a] GnRHa[b]	Ovarian tissue cryopreservation
Postpubertal	GnRHa Ovarian transposition Ovarian tissue cryopreservation[a]	Embryo cryopreservation Mature oocyte cryopreservation Ovarian tissue cryopreservation

[a] Long-term function uncertain.
[b] Experimental/benefit uncertain.

Recently, several meta-analyses have evaluated the role of GnRHa for ovarian function protection in women with early-stage breast cancer. In a systematic review, the rate of premature ovarian insufficiency was 30.9% in women receiving chemotherapy; in comparison, the rate decreased by almost half to 14.1% in women who received GnRHa [50]. This finding was confirmed in another review in which GnRHa administration was associated with a positive impact on ovarian function preservation when compared to women who received chemotherapy alone (odds ratio 1.83) [49]. When assessing resumption of menstrual cycles, women who received GnRHa had higher recovery rates at 6 months (odds ratio 2.4) and 1 year (odds ratio 1.85) [55]. Lambertini et al. reported that amenorrhea rates at 2 years were 18.2% in women who received GnRHa compared to 30% at 1 year [50]. Of note, the benefit of GnRHa seems to be greater in women of age less than 40 years [51].

On the contrary, women who received chemotherapy with or without GnRHa for lymphoma did not have improvement in rates of premature ovarian insufficiency [52]. However, they did note that factors including age, regimen for stem cell transplant, and dose of cyclophosphamide were associated with ovarian insufficiency [52].

Another measurement of ovarian function that has been reported is post-treatment pregnancy rates. In women with early-stage breast cancer who received GnRHa, spontaneous pregnancy rates of 10.3% were reported compared to 5.5% in women who received chemotherapy alone [50]. Leonard and colleagues also reported higher rates of pregnancy (odds ratio 1.85) in women who received GnRHa [51]. Similar to ovarian function, this finding was not confirmed in women who were receiving therapy for lymphoma. In this series of 67 patients, pregnancy rates were not statistically different in those who received GnRHa (53%) compared to those who did not (43%) [52].

Although variable with several factors contributing to these outcomes, the role of GnRHa may offer potential ovarian protection in women undergoing cytotoxic therapy. Most importantly, the administration of GnRHa has not demonstrated a negative impact on disease-free or overall survival and is a low-risk intervention [50]. On the basis of these findings, although treatment should be individualized, GnRHa should be considered in all women of reproductive age undergoing treatment with gonadotoxic chemotherapy.

Women undergoing radiation

As previously discussed, the ovaries are exquisitely radiosensitive and exposure as low as 2–20 Gy may result in loss of function [47,56]. Women who require pelvic or lower abdominal radiation often receive doses of 42 Gy or higher and are, therefore, at risk for loss of ovarian function [57].

Options for ovarian preservation are predominantly surgical and also include innovative nonsurgical techniques. Although ovarian transplantation has been studied, the predominant surgical option for ovarian protection is ovarian transposition or oophoropexy. The most common surgical technique for ovarian transposition suspends the ovaries above the level of the pelvic brim in the paracolic gutters, outside the pelvic radiation field. The medial approach, in which the ovaries are placed posterior to the uterus, may be beneficial when radiation is delivered to the lateral aspect of the pelvis [58–61].

Although these techniques decrease the radiation exposure to the ovaries, the success rates vary widely [62–64]. As mentioned, age is a major factor, and studies have shown that women above the age of 40 years have higher reported rates of ovarian failure despite ovarian transposition than younger women [63–67]. In one series of women receiving at least 42 Gy of pelvic radiation, for a variety of tumors, ovarian transposition failure was reported as low as 10–14% [57]. However, in another series of 127 women with Hodgkin's lymphoma, 10 years following the administration of pelvic radiation, ovarian transposition did not significantly improve the rate of premature ovarian insufficiency [68]. A systematic review/meta-analysis from 2014 of 24 studies reported that women who underwent ovarian transposition with surgery only compared to surgery and radiation therapy had ovarian function preservation in 90% and 65% of cases, respectively [69]. Although prospective studies are lacking, premenopausal women, who are appropriate candidates for preservation of ovarian function, should be offered surgical consultation for discussion of risks and benefits of ovarian transposition.

In addition to retained ovarian function, pregnancies following pelvic radiation and ovarian transposition have been reported [59,64]. However, it is important to recognize that, although more radioresistant than the ovaries, radiation exposure to the uterus may further affect the ability to carry a pregnancy. Therefore, patients should be counseled about this risk and offered consultation for fertility options if desired (discussed below).

Nonsurgical techniques to preserve ovarian function in women undergoing radiation therapy have also been described and are limited. As a proposed alternative to ovarian transposition is the shielding of the ovaries during radiation therapy. However, this technique has limitations including inaccurate shielding, obscuring orthopedic landmarks, and affecting the delivery of radiation therapy to targeted areas [70]. Thus, in general, ovarian shielding is not a favored approach. A simple technique that has been reported is to fill the urinary bladder at the time of treatment. A full bladder may manually shift the ovaries out of the pelvis, thereby decreasing radiation exposure [70]. Although efficacy may be unpredictable, this is an inexpensive and simple technique to employ and hence may be considered.

An experimental area of study is the administration of radioprotective agents. One agent that has been evaluated is sphingosine-1-phosphate (S1P), which is an antiapoptotic factor. When administered to rhesus monkeys followed by 15 Gy of pelvic radiation, S1P shielded the ovaries from the radiotoxic effects as noted by the presence of more ovarian follicles in the treated group than in the untreated counterparts [71]. Although the investigation of agents like S1P and others shows promise for their potential role of ovarian protection in women undergoing radiation therapy, further studies are warranted.

Fertility preservation

The assessment of interest in fertility preservation, impact of oncologic therapy on reproductive function, and subsequent options for future fertility should be initiated as soon as possible in young women diagnosed with cancer. For minors, the parents and/or guardians must be engaged in decision-making for fertility preservation. Occasionally, consultation with a medical ethicist to guide decision-making may be beneficial. When appropriate, early referral for consultation and treatment to reproductive specialists should be made if any desire for fertility preservation may exist. Aside from the options previously discussed, fertility-specific interventions include cryopreservation techniques such as embryo/oocyte or ovarian tissue cryopreservation. These practices may preserve a woman's own gamete potential for future pregnancy consideration. However, many of these techniques can be expensive and require consultation and communication of oncologic care plan with a reproductive specialist. Despite the significant impact that oncologic therapy may have on ovarian reproductive function, women should be reassured that oncologic therapy is not mutagenic to the ovaries and offspring of women who conceive after cancer treatment do not have high rates of congenital abnormalities [22–24].

Embryo or oocyte cryopreservation

The use of embryo or oocyte cryopreservation has been well described and should be considered the standard of care in postpubertal women [72]. Cryopreservation techniques of oocytes or embryos allow for future implantation in either the patient or a gestational carrier. The utilization of assisted reproductive technologies requires a reproductive endocrinology specialist, and early consultation should be considered.

Of note, there are several important considerations for either embryo or oocyte cryopreservation, of which patients and clinicians should be aware. First, ovarian stimulation for oocyte retrieval can take several weeks to perform. The delay in initiating therapy for ovarian stimulation must be considered when treatment is required to begin expeditiously. When rapid initiation of therapy is required, there have been descriptions of accelerated procedures for oocyte retrieval, but these techniques should be discussed on an individualized basis [73,74]. Regardless of timing, ovarian stimulation for oocyte retrieval should be initiated before chemotherapy administration because the efficacy of in vitro fertilization is reduced after administration of therapy [75,76]. Next, when counseling regarding cryopreservation options, it is also important to consider if the woman has a partner for insemination or willingness to use donor sperm. This is important because embryo preservation can only occur with fertilized oocytes. When embryo cryopreservation is not able to be performed, cryopreservation of mature oocytes may be considered for women planning to undergo oncologic therapy. It is important to acknowledge that oocyte cryopreservation has lower success rates and is more technically challenging [77–79]. However, in certain circumstances, oocyte cryopreservation may be the most appropriate option, and this technique must be considered for women desiring future fertility [72]. Finally, children with cancer present legal and ethical issues. Healthcare autonomy and appropriate informed consent from the guardian(s) are necessary. Assistance from a medical ethicist and local judicial considerations may assist with providing appropriate reproductive care for minors [80].

Ovarian tissue cryopreservation

A potential exciting emerging option for selected patients may be cryopreservation of ovarian tissue with subsequent reimplantation [81]. Recent data suggest that success rates with cryopreserved ovarian transplantation are promising and should be considered as a viable option for women seeking fertility preservation [82]. A recent meta-analysis from Pacheco reported live birth and ongoing pregnancy rates of 37.7% [83]. Ovarian tissue cryopreservation has the additional benefits of not requiring hormonal stimulation and no need for insemination of oocytes and is the only option that can be performed in prepubertal girls. As with embryo and oocyte retrieval, ovarian tissue should be harvested before the initiation of chemotherapy and may be accomplished with either a complete or a partial oophorectomy [84]. Transplantation to the patient can be accomplished by several techniques, with reintroduction of the tissue to the preexisting ovarian tissue or to a new location such as the forearm [85]. It is notable that ovarian cryopreservation with reimplantation is the only method that allows for fertility preservation as well as hormonal restoration. Although there have been reports of long-term function, this technique is still in early development, and further evaluation will confirm its true utility [88].

Before ovarian preservation techniques or reimplantation, clinicians must also consider hereditary cancer syndromes that increase the risk for development of ovarian cancer, such as BRCA mutation carriers or women who may have metastatic ovarian involvement. In addition to malignant transformation of the transplanted tissue, microscopic metastatic disease not identified at the time of harvest is a concern, although this concern is mostly hypothetical [82,86,87].

Despite the known impact of oncologic therapy on ovarian function, it is important to highlight the lack of counseling or interventions that are utilized. For example, Rentea and colleagues reviewed discussions regarding fertility preservation in 53 patients who received pelvic radiation. The authors noted that 32% of women had evidence of premature ovarian failure, and only 17% had a documented discussion regarding fertility preservation [90]. Another recent retrospective report from Moravek et al. found that only 10% of patients who underwent fertility preservation techniques returned to use their cryopreserved specimens [89]. Therefore, providers and cancer programs should consider the development of multidisciplinary fertility preservation teams for urgent consultation and protocols regarding treatment options that affect ovarian function or fertility.

Summary

Oncologic therapy can substantially impact ovarian function, which in turn can hamper normal development through puberty and reduce prolonged health benefits. Considerations regarding fertility and the health benefits of normal hormonal function should be part of a woman's oncologic consultation. Clinicians should be prepared to discuss the acute and chronic impacts therapy will have on ovarian function. Although interventions for ovarian protection are limited, medical therapies such as use of GnRHa should be considered in all women of reproductive age undergoing treatment with gonadotoxic chemotherapy. Surgical referral for those patients who are planning to have pelvic radiation for ovarian transposition should also be offered when appropriate. Perhaps, the technique that holds the most promise to reduce the morbidity of ovarian failure in patients with cancer is ovarian tissue cryopreservation with subsequent transplantation.

Practice points

- Young women and girls should be counseled regarding premature ovarian failure and infertility when discussing oncologic care
- Strategies to reduce the impact of oncologic therapy on ovarian function should be offered when appropriate
- Early consultation with a reproductive or oncofertility specialist is essential, and a multidisciplinary approach should be considered
- Ovarian cryopreservation is a promising technique and the only available fertility option for prepubertal girls as well as the only fertility preservation technique that has resumption of the hormonal function of the ovary

Research agenda

- Feasibility of incorporating oncofertility consultation programs for all young women diagnosed with cancer who require therapy that affects ovarian function
- Studies prospectively evaluating the impact of therapies on ovarian function
- Novel techniques (e.g., ovarian preservation and transplantation) and agents for ovarian protection from gonadotoxic therapy

Conflicts of interest

The authors have no conflicts of interest.

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None.

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