Current Treatment Options in Oncology
DOI 10.1007/s11864-012-0183-7

Oncofertility (JS Jeruss, Section Editor)

Pediatric and Young Adult Patients and Oncofertility

Katherine E. Dillon, BA
*Clarisa R. Gracia, MD, MSCE**

Address
*University of Pennsylvania, 3701 Market Street, Suite 800, Philadelphia, PA 19104, USA
Email: cgracia@obgyn.upenn.edu

Keywords Oncofertility · Reproductive risks · Fertility Preservation · Gonads

Opinion statement

With improving survival rates for pediatric and young adult cancer patients, considerations regarding the long-term effects of therapy have become more important. Cancer therapies are known to pose reproductive risks, though the effects may be unpredictable. All at-risk patients should have a discussion about potential treatment-related infertility before the onset of cancer therapy, and should be offered appropriate fertility preservation options. Embryo and sperm cryopreservation are considered standard therapy, though oocyte cryopreservation is gaining acceptance. Ovarian tissue cryopreservation, while still experimental, is showing great promise. It is the only option currently available to prepubertal girls. No fertility preservation options exist for prepubertal boys though some institutions may offer experimental testicular tissue cryopreservation.

Introduction

With advancements in the diagnosis and treatment of cancer in pediatric and adolescent patients, increasing numbers of survivors in this age group are looking toward a future as productive adults. For many this includes consideration of future fertility. Given that cancer treatments have been shown to impair normal pubertal development and may lead to infertility, it is imperative that oncologists discuss the issue of fertility preservation with patients prior to the onset of cancer treatment. This requires that clinicians be informed about the preservation options available and the reproductive challenges patients may face.

This review article aims to use the most up-to-date data to inform the clinician about the effects of various cancer treatments on reproductive potential and the options for fertility preservation prior to cancer therapy. It will focus on important recent advancements made in the field of oncofertility and will highlight future directions for fertility preservation technologies.

Cancer in children and young adults

The most common cancers in children are leukemias, followed by central nervous system malignancies, lymphomas, soft tissue sarcomas, renal cancer (Wilm's Tumor) and bone tumors, in that order [1]. Treatments often involve a combination of surgery, radiation therapy, chemotherapy with alkylat-

Published online: 16 March 2012

ing agents, or allogenic bone marrow transplant. Late effects of cancer are gaining more attention since over 80% of childhood cancer patients survive at least five years [2] and an estimated one in 640 adults ages 20–39 is currently a long-term childhood cancer survivor [1]. However, it is a challenge to balance curative therapy while reducing the risks to fertility. This is especially difficult due to ever-changing cancer regimens and a lack of prospective data concerning their effects on fertility outcomes.

One of the recognized challenges in studying the reproductive risks of cancer therapy is that outcomes such as fertility are difficult to capture. An individual's fertility depends on many factors including the availability of a fertile partner of the opposite sex, and a desire to conceive. The gold standard epidemiologic method to study fertility is to conduct prospective "time to pregnancy" studies. Such studies are generally not feasible in conditions where the exposure (cancer therapy) is relatively rare. Therefore, most studies have assessed other related outcomes such as menstrual function or reported pregnancy after cancer treatment. In females, measures of ovarian reserve, such antral follicle counts and ovarian volume assessed by ultrasound, and serum measures of inhibin B, anti-Mullerian hormone (AMH), estradiol, and follicle-stimulating hormone (FSH) have also been useful proxy outcomes.

In the field of pediatric oncofertility most of the large-scale studies with epidemiologic data stem from findings from the childhood cancer survivorship study (CCSS), a large retrospective cohort study assessing a variety of late effects of childhood cancer. The CCSS is the largest cohort study of childhood and adolescent cancer survivors with 20,720 previously untreated patients with a new diagnosis before the age of 21 enrolled. It is important to recognize that the effect of cancer therapies on an individual's reproductive function can be unpredictable. Nonetheless, the available data on the reproductive risks of cancer therapies will be reviewed, and is summarized in Table 1.

Treatment effects in females

Pelvic radiation

The ovaries are particularly sensitive to damage from cancer treatments due to the finite number of un-renewable germ cells (follicles) present in the ovary. The ovary begins producing oocytes before birth and oocyte count peaks at 20 weeks gestation. After this peak, progressive follicular atresia occurs. Radiotherapy can cause ovarian failure by accelerating follicular atresia and destruction of the follicular pool. Earlier studies have shown that females treated with pelvic radiation doses in excess of 2 gray (Gy) are at high risk of permanent ovarian failure [3]. Using this data, Wallace et. al developed a mathematical model that estimates the dose of ovarian radiation necessary to cause ovarian failure taking into account age at treatment. For example, the estimated mean radiation dose to the ovaries needed to cause sterilization is 16 Gy at age 15, while a dose of only 12 Gy is required at age 30 [4]. Radiotherapy can also have deleterious effects on the uterus as it causes scarring and diminished uterine blood flow in a dose-dependent fashion [5], resulting in decreased uterine volume [6, 7].

Recent studies have examined the reproductive risks associated with pelvic radiotherapy in pediatric and adolescent cancer patients and have reported more relevant reproductive outcomes such as reports of pregnancy. For example, data from the CCSS demonstrated that the relative risk of achieving pregnancy at least five years post-treatment in female childhood cancer survivors exposed to 5 to 10 Gy of radiation to the pelvis was 0.56, and dropped to 0.18 for exposure greater than 10 Gy when survivors were compared to a similar-age sibling cohort [8••]. While the relative risks reported in this study clearly highlight the adverse effects of radiation

Table 1. Reproductive risks of cancer therapy in pediatric and young adult patients

Risk	Females	Males
High	>10 Gy Pelvic Radiation	Testicular Radiation
	Hypothalamic Pituitary Radiation	Hypothalamic Pituitary Radiation
	Hematopoetic Cell Transplantion	Hematopoetic Cell Transplantation
	Total Body Irradiation	Total Body Irradiation
	Chemotherapy with Alkylating Agent Dose ≥2[a]	Chemotherapy with Alkylating Agent Dose ≥2[a]
Medium	5–10 Gy Pelvic Radiation	Platinum-containing drugs
	Chemotherapy with Alkylating Dose >0[a]	Chemotherapy with Alkylating Dose >0[a]
Low	<4 Gy Pelvic Radiation	Non-Alkylating Chemotherapy
	Non-Alkylating Chemotherapy	Anti-Metabolites
	Anti-metabolites	

[a]Alkylating Agent Dose calculated according to Green et. al. [8••].

exposure, it is important to recognize the limitations of the data when counseling patients. This study examined rates of conceiving a pregnancy 5 years or more after diagnosis compared to a sibling cohort so as to match for socioeconomic status and education. It is possible that having a cancer diagnosis itself influenced the decisions to pursue pregnancy or the timing of pregnancy in survivors. Information about whether patients attempted pregnancy was not in the study, though the analysis did control for marital status. Moreover, information on menstruation cycles or reported infertility was not available.

A retrospective French study of childhood cancer survivors over the age of 18 (median age 27 years) found that direct pelvic irradiation was the most significant risk factor for subfertility, defined as no spontaneous menstruation or pregnancies. The odds of subfertility were 17.6 in the exposed compared to the unexposed group [9•]. When controlling for adjuvant therapy, radiation doses to the reproductive organs of less than 4 Gy were not significantly associated with subfertility [9•]. The study also suggests that ovarian transposition or shielding may protect reproductive function. Limitations of this study include the convenience sample with small subgroup numbers and the suboptimal definition of subfertility [10, 11].

Not only does exposure to pelvic radiation increase risk of infertility, pelvic irradiation is also associated with adverse pregnancy outcomes. Another CCSS study of 1281 female survivors demonstrated an association between pelvic irradiation exposure prior to menarche and subsequent stillbirth or neonatal death [12••]. Compared to survivors who did not receive radiotherapy, those exposed to 2.5–9.9 Gy of radiotherapy had a relative risk of 5.8 for stillbirth or neonatal death while those exposed to more than 10 Gy had a relative risk of 19. A previous study also demonstrated that pelvic irradiation increased the risk of preterm birth for female childhood cancer survivors [13]. Patients with a history of pelvic radiation therapy should be counseled about the perinatal risks of pregnancy and may consider using a gestational carrier if pregnancy is unsuccessful.

Hypothalamic pituitary radiation

Hypothalamic-pituitary radiation causes destruction and fibrosis of the pituitary and can lead to significant hypothalamic-pituitary dysfunction.

With respect to reproduction, an intact hypothalamic-pituitary axis is required for ovulation and unassisted conception. Signs of hypothalamic dysfunction include amenorrhea, elevated prolactin and suppressed levels of gonadotropins. It has previously been reported that the relative risk for a survivor achieving pregnancy after receiving a radiation dose of 3 Gy or more to the hypothalamic-pituitary axis (HPT) was 0.61 when compared to a similar-age sibling cohort [8••]. A more recent report which included patients who were not exposed to ovarian radiation and controlled for relevant demographic variables including age at diagnosis and marital status, suggests that even lower doses pose reproductive risks. The hazard ratio of achieving pregnancy after 2.2–2.7 Gy to the HPT was 0.67 compared to unexposed survivors [14•]. This study demonstrates that even very low levels of radiation to the pituitary impair fertility. Importantly, pituitary irradiation does not appear to be associated with adverse perinatal outcomes [12••].

Chemotherapy

Chemotherapeutic agents, particularly alkylating agents, cause damage to the ovary by cross-linking DNA and introducing single-stranded DNA breaks. Histologic evaluation of the ovaries in patients exposed to chemotherapy after treatment demonstrate a range of findings, from decreased numbers of follicles to absent follicles and stromal fibrosis [15]. Age is one of the most important factors in determining the gonadotoxicity of treatment since ovarian reserve and follicle number decrease with age. At older ages lower doses of chemotherapy are required to produce ovarian failure. Independent of age, there is no evidence that the prepubertal ovary is protected from damage from chemotherapy.

It has been demonstrated that the ovary is very susceptible to chemotherapeutic treatments, particularly alkylating agents, in a dose-dependent fashion. In one study, the relative risk of a female survivor of childhood cancer reporting pregnancy was inversely related to the cumulative alkylator exposure (typically summarized as alkylating agent dose, AAD) [8••]. For example, an AAD score of three had a relative risk of 0.72 of pregnancy and an AAD score of four had a relative risk of 0.65 of pregnancy compared to survivors who received no alkylators. Additionally, the chemotherapeutic agents CCNU and cyclophosphamide were independently associated with impaired fertility in a dose-dependent fashion [8••].

It is clear that not all treatments are equally gonadotoxic. A study of pediatric patients treated for Hodgkin's lymphoma (HL) demonstrated that measures of ovarian reserve, such as AMH, were significantly lower in patients treated with ABVD or EBVD and MOPP therapy compared to ABVD or EBVD without MOPP therapy [16]. Additionally, a current study in Europe is comparing procarbazine and dacarbazine for treatment of HL in pediatric patients with the hypothesis that dacarbazine is less harmful to the ovary but just as efficacious as procarbazine [17].

It does not appear that alkylating drugs increase the risk of stillbirth or neonatal death among the children of female survivors, even in those who received the highest doses [12••]. Thus, there is currently no evidence that having received previous chemotherapy results in genetic defects in offspring.

Bone marrow transplantation

Hematopoietic cell transplantation (HCT) poses especially high reproductive risks since conditioning regimens often require high-dose chemotherapy and/or total body irradiation (TBI). In post-pubertal females, ovarian failure has been observed in 65–84% of pediatric transplant recipients [18, 19]. In pre-pubertal females, incomplete pubertal development or pubertal failure has been reported in approximately 57% of females following HCT [20]. The reproductive risks appear to be higher in conditioning regimens which include cyclophosphamide with busulfan, and those that require TBI [21].

Treatment effects in males

Testicular radiation

The male testes are responsible for spermatogenesis and steroidogenesis. Within the testes spermatogonial germ cells, supported by Sertoli cells, generate sperm while the Leydig cells produce testosterone. With respect to cancer therapies, it is important to understand that spermatogonia are more sensitive to insults than Leydig cells. Therefore, male cancer survivors are more likely to experience infertility than problems with pubertal development or sexual function.

Testicular tissue is extremely sensitive to radiation, even more so than the ovary. Radiation doses as low as 0.1 Gy can cause oligospermia, and reversible azospermia has been identified at doses as low as 0.35 Gy [22]. Though the testes are rarely directly radiated, even exposure due to scatter radiation can have reproductive consequences. As mentioned, the Leydig cells are somewhat less sensitive, and doses of at least 12 Gy are necessary to impair pubertal development and sexual function [23]. Thus after radiation, puberty may proceed normally even in the setting of oligospermia and is not a reliable marker of recovered fertility.

Data from the CCSS demonstrate that doses of radiation over 7.5 Gy are associated with a significantly lower likelihood of fathering a child, with a hazard ratio of 0.12 compared with sibling controls [24••]. This study is limited by the assessment of reproductive choices.

There is some theoretical concern that cancer therapies have the potential to cause mutagenesis in the testes and therefore may impact the health of offspring. The CCSS has not found evidence of increased genetic problems, stillbirth, or neonatal death in men treated with gonadal radiation as children [12••].

Chemotherapy

Chemotherapy, especially alkylating agents, also causes significant damage to testicular tissue in an agent-specific and dose-dependent manner. Antimetabolite therapy such as methotrexate and mercaptopurine appear to have no effect on male fertility, while cisplatin-based regimens temporarily impair spermatogenesis with recovery shown in a significant number of patients [25].

Data from the CCSS demonstrated that males with Hodgkin's lymphoma were the least likely to father a child (hazard ratio (HR) 0.34, confidence interval (CI) 0.28–0.41) compared to other types of cancer, while those

diagnosed with Wilms tumor or neuroblastoma were as likely as healthy siblings to father a pregnancy. Moreover, there was a dose–response effect between the dose of alkylating agent and reduced likelihood to father a child (HR 0.67, CI 0.51–0.88 for an AAD score of 2 and a HR 0.16, CI 0.08–0.32 for an AAD score of 6–11) [24••]. Specific chemotherapeutic agents appear to impair fertility, including procarbazine in the second or third dose tertile and cyclophosphamide in the third dose tertile [24••].

It is important to note that pregnancies resulting from assisted reproductive technologies were not included in this study. Therefore it is possible that higher pregnancy rates may be achieved utilizing techniques such as in vitro fertilization and intracytoplasmic sperm injection. Additionally, this study examined rates of fathering a pregnancy five years or more after diagnosis compared to sibling controls. It is possible that having a cancer diagnosis influenced the decisions surrounding whether to pursue pregnancy and timing of pregnancy. Information about this decision-making was not collected in the study, though the analysis was controlled for marital status.

It is also important to note that male survivors without high-risk exposures (including radiotherapy to the testes greater than 7.5 Gy, AAD score greater than or equal to 2, or treatment with procarbazine or the third tertile of cyclophosphamide) were just as likely as their siblings to father a child [24••].

Pregnancies in partners of male cancer survivors appear to be reassuring. The CCSS study has not found an increase in stillbirths or neonatal deaths among children of males who received chemotherapeutic agents, even when examining higher tertile doses of the drugs [12••].

Bone marrow transplantation

As in females, hematopoietic cell transplantation (HCT) poses especially high risks to fertility, including delayed puberty, as it requires exposure to high-dose chemotherapy and/or total body irradiation before the procedure. Azoospermia in post-pubertal boys has been shown in 48–85% of those undergoing HCT [21, 26, 27]. Incomplete pubertal development or pubertal failure has been reported to occur in approximately 53% of prepubescent males exposed to HCT [20]. Similar to females, the risk of delayed puberty is dependent on the conditioning regimen administered, with the highest risk protocols including a combination of cyclophosphamide and busulfan or TBI [21]

The need for fertility preservation counseling

Given the clear risks to fertility associated with many therapies, it is imperative that clinicians discuss the fertility risks and preservation options with patients and families prior to the onset of treatment. Often clinicians caring for cancer patients are hesitant to initiate such conversations, citing reasons such as insufficient knowledge, lack of time to discuss the issue with patients, or perceptions that the patient cannot delay treatment [28]. A recent study in women age 18 or older found that pretreatment infertility counseling by a fertility specialist and an oncologist resulted in lower regret than counseling by an oncologist alone [29]. These issues are even more

important for the pediatric and adolescent population who often feel that they are not given enough say in their medical choices. Importantly, the ability to have biological children greatly effects the quality of life of childhood cancer survivors in adulthood; it has been demonstrated that a perceived loss of fertility is associated with lower marriage rates and increased divorce rates in this population [30].

Furthermore, the American Society of Clinical Oncology (ASCO) and the American Society of Reproductive Medicine (ASRM) have both issued guidelines in recent years. The ASRM guidelines stipulate that 'physicians should inform cancer patients about options for fertility preservation and future reproduction prior to treatment', and specifically that 'parents may act to preserve the fertility of cancer patients who are minors if the child assents and the intervention is likely to provide net benefits to the child [31]. These guidelines were reinforced one year later when ASCO recommended that clinicians should address issues of infertility at the earliest possible opportunity [32]. A schematic of the fertility preservation options available is presented in Fig. 1.

Fertility preservation options

Females

Embryo cryopreservation

The options for pediatric and adolescent female cancer patients are somewhat limited compared to their adult counterparts. Overall, the established and most successful method of fertility preservation is embryo cryopreservation. However, this requires that the patient be postpubescent and either have a partner or be willing to use donor sperm.

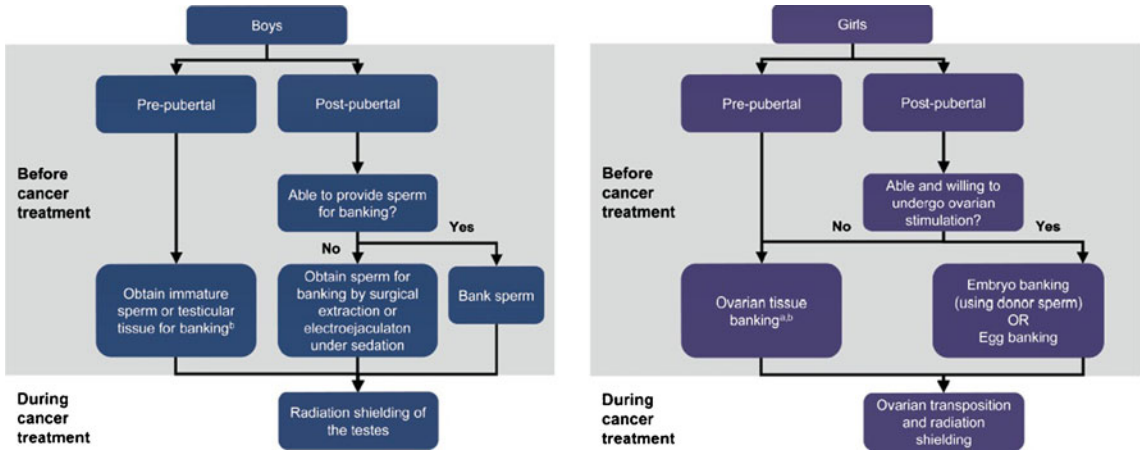

Figure 1. Fertility preservation options for children and young adults diagnosed with cancer ***a*** *Not an option if there is a high risk of ovarian metastases.* ***b*** *Experimental—only performed as part of a clinical study approved by an IRB.* Used with permission from SaveMyFertility.org.

Ovarian stimulation and oocyte retrieval can take 2–5 weeks and may delay treatment of some malignancies. While embryo cryopreservation has a success rate of 30–40% per transfer [33, 34], this may not be a realistic approach for girls and young single women.

Oocyte cryopreservation

Though still considered experimental, oocyte cryopreservation is another option that can be offered and conducted under a research protocol overseen by an Institutional Review Board. Oocyte cryopreservation has the advantage of eliminating the need for a partner or donor sperm, offering females reproductive autonomy. However, it still requires that the patient be post-pubertal and undergo ovarian stimulation and oocyte retrieval. Over 900 live births have been reported from oocyte cryopreservation and outcomes appear generally reassuring [35]. Often adolescent patients present with cancers such as leukemia and generally need immediate cancer therapy. However, in post-pubescent females with available time, oocyte cryopreservation may be the preferred method of fertility preservation. While historically success rates of oocyte cryopreservation have been lower than embryo cryopreservation, recent improvements in cryopreserved techniques such as vitrification have resulted in dramatic improvements in success. Indeed some studies suggest that pregnancy rates are approaching those for embryo cryopreservation and even fresh IVF [35–37]. There is evidence that more than 50% of fertility clinics in the United States are offering oocyte cryopreservation [36].

Ovarian tissue cryopreservation

Ovarian tissue cryopreservation is an experimental technique that shows great promise. The procedure can be performed emergently, minimizing delay in cancer treatment, and it is the only option available for prepubescent girls. The procedure involves removing a piece of ovarian cortical tissue or the whole ovary either laparoscopically or through laparotomy. Typically, ovarian cortical strips are cryopreserved and can subsequently be thawed and transplanted later (frozen-thawed autologous tissue transplanation has resulted in 14 live births to date [38]). Alternatively, follicles extracted from ovarian tissue may, in the future, be matured in vitro (IVM) to produce mature oocytes that can be fertilized and transferred into the uterus at a later time. While this latter method is still experimental and has not yet resulted in any human live births, continued investigation is being conducted in human models [39, 40]. IVM would be preferable in cases where there is a high concern for reseeding cancer. This is crucially important as there is a potential risk when reimplanting tissue from a patient with a hematologic disease. This risk appears to be significant in patients with leukemia or other malignancies that may have spread to the ovary [41•]. A recent publication by Dolmans et al. highlights this risk. Investigators transplanted thawed ovarian tissue from 18 patients with leukemia into mice. Analyzed tissue demonstrated molecular evidence

of cancer in 7/12 cases of acute lymphoblastic leukemia (ALL) and 2/6 chronic myelogenous leukemia transplants. When mice were sacrificed after six months and gross tumors were found in 4 mice, all had received ovarian transplants from ALL patients [41•]. Given that ovarian tissue cryopreservation requires surgery under general anesthesia, whenever possible ovarian tissue cryopreservation should be coupled to another necessary surgical procedure, often a central venous access procedure or tumor excision. In our own practice, we have performed 12 cases of ovarian tissue cryopreservations in female patients under the age of 20. Four had central nervous system tumors, two had acute myeloid leukemia, two had Ewing's sarcoma, one had HL, one had myelodysplastic syndrome, one had rhabdomyosarcoma, and one had sickle-cell disease. Of these, 6 (50%) had received prior chemotherapy and were planning for stem cell transplantation, 3 also had ovarian transposition performed at the time of the biopsy, and one had already failed oocyte retrieval. There have been no surgical or post-operative complications, but one patient has died from disease recurrence. No patients have yet requested that the tissue be used clinically.

Oophoropexy

Other options for females include oophoropexy or fertility-sparing cancer surgery. Oophoropexy involves surgically displacing the ovaries out of the radiation field (often above the pelvic brim or behind the uterus) to protect against damage from radiation exposure. This requires that the reproductive endocrinologist work closely with the radiation oncologist to determine placement that minimizes the radiation exposure. Potential complications include pelvic pain and fallopian tube damage [42].

Ovarian suppression

Temporary suppression of ovarian function during chemotherapy using gonadotropin-releasing hormone analogues (GnRH) has been shown to reduce damage in animal models [43]. However, the exact mechanism is not understood. Human studies suggest that menstrual cycles may be more likely to resume in patients treated with GnRH as compared to those not. However, studies are limited by small samples and inappropriate comparison populations. Large prospective trials are lacking and randomized controlled trials are needed to address this controversial issue.

Hormone replacement therapy

Prepubertal cancer patients with delayed pubertal development due to ovarian failure should receive a physiologic regimen of hormone replacement therapy to ensure optimal development of secondary sex characteristics and adult stature [20]. After menarche, early loss of ovarian function is associated with menopausal symptoms and long term health risks including cardiovascular disease and osteoporosis. While the optimal method of hormone replacement therapy is not clear, some form ofhormone therapy is recommended since it effec-

tively treats menopausal symptoms and improves bone mineral density [44, 45].

Males

Sperm cryopreservation

For males, sperm cryopreservation through masturbation is an established and successful method of fertility preservation prior to cancer treatment. It is non-invasive, relatively inexpensive, and can be performed without any delay in the initiation of cancer therapy. All adolescent and young adult males should be offered sperm cryopreservation prior to the onset of treatment. Because sperm production begins around the age of 12 or 13 in males, adolescent boys who are unable to produce semen through masturbation may undergo penile vibratory stimulation or rectal electrostimulation under anesthesia [46]. Additionally, sperm may be collected via testicular or epididymal aspiration under anesthesia if spermatogenesis is established. After cryopreservation, stored sperm may be used for insemination or in vitro fertilization (with intracytoplasmic sperm injection if counts are low) [47, 48].

Testicular tissue cryopreservation

For pre-pubescent males, the only options available are experimental and require further development through basic science research. Cryopreservation and subsequent in vitro maturation or transplantation of spermatogonial stem cells and testicular tissue has theoretical potential but cannot currently be used in a clinical setting. A pilot study at The Children's Hospital of Philadelphia reports evidence of acceptability and no cases of peri- or post-operative complications from testicular tissue biopsy and cryopreservation [49]. There is no conclusive evidence that GnRH analogues are effective in protecting against testicular damage from chemotherapy in males [32].

Future directions

Oncofertility in the pediatric and adolescent populations continues to evolve. We must work together in the basic, translational, and clinical science communities to make progress in minimizing the gonadotoxicity of cancer treatments, improving and developing novel fertility preservation techniques, prospectively monitoring and detecting subfertility in cancer survivors, and providing appropriate counseling to patients and their families about these issues. This demands a comprehensive team approach including oncologists and reproductive endocrinologists working together to provide the best possible outcome for each young patient.

Disclosure

No potential conflicts of interest relevant to this article were reported.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Stat bite: Childhood cancer survival, 1975–2003. J Natl Cancer Inst. 2006;98:883.
2. Hewitt M, Rowland JH, Yancik R. Cancer survivors in the United States: age, health, and disability. J Gerontol Biol Sci Med Sci. 2003;58:82–91.
3. Wallace WH, Thomson AB, Kelsey TW. The radiosensitivity of the human oocyte. Hum Reprod. 2003;18:117–21.
4. Wallace WH, Thomson AB, Saran F, Kelsey TW. Predicting age of ovarian failure after radiation to a field that includes the ovaries. Int J Radiat Oncol Biol Phys. 2005;62:738–44.
5. Critchley HO, Wallace WH. Impact of cancer treatment on uterine function. J Natl Cancer Inst Monogr. 2005;34:64–8.
6. Holm K, Nysom K, Brocks V, Hertz H, Jacobsen N, Muller J. Ultrasound B-mode changes in the uterus and ovaries and Doppler changes in the uterus after total body irradiation and allogeneic bone marrow transplantation in childhood. Bone Marrow Transplant. 1999;23:259–63.
7. Wo JY, Viswanathan AN. Impact of radiotherapy on fertility, pregnancy, and neonatal outcomes in female cancer patients. Int J Radiat Oncol Biol Phys. 2009;73:1304–12.
8. •• Green DM, Kawashima T, Stovall M, Leisenring W, Sklar CA, Mertens AC, Donaldson SS, Byrne J, Robison LL. Fertility of female survivors of childhood cancer: a report from the childhood cancer survivor study. J Clin Oncol. 2009;27:2677–85.

This study from the CCSS cohort presents excellent epidemiologic data on the relative risk of females achieving pregnancy after receiving cancer therapy in childhood. The data examined included all doses and volumes of radiation therapy received and all chemotherapeutic agents including cumulative doses of alkylating agents.

9. • Sudour H, Chastagner P, Claude L, Desandes E, Klein M, Carrie C, Bernier V. Fertility and pregnancy outcome after abdominal irradiation that included or excluded the pelvis in childhood tumor survivors. Int J Radiat Oncol Biol Phys. 2010;76:867–73.

An important recent retrospective study demonstrating a dose–response effect of pelvic irradiation on subfertility in a female childhood cancer survivor population.

10. Larsen EC, Muller J, Schmiegelow K, Rechnitzer C, Andersen AN. Reduced ovarian function in long-term survivors of radiation- and chemotherapy-treated childhood cancer. J Clin Endocrinol Metab. 2003;88:5307–14.
11. Letourneau JM, Ebbel EE, Katz PP, Oktay KH, McCulloch CE, Ai WZ, Chien AJ, Melisko ME, Cedars MI, Rosen MP. Acute ovarian failure underestimates age-specific reproductive impairment for young women undergoing chemotherapy for cancer. Cancer. 2011.
12. •• Signorello LB, Mulvihill JJ, Green DM, Munro HM, Stovall M, Weathers RE, Mertens AC, Whitton JA, Robison LL, Boice Jr JD. Stillbirth and neonatal death in relation to radiation exposure before conception: a retrospective cohort study. Lancet. 2010;376:624–30.

An important study from CCSS cohort demonstrating that pelvic irradiation in females is associated with adverse pregnancy outcomes, while pituitary irradiation, irradiation of the testes, and chemotherapy with alkylating agents were not found to be risk factors.

13. Signorello LB, Cohen SS, Bosetti C, Stovall M, Kasper CE, Weathers RE, Whitton JA, Green DM, Donaldson SS, Mertens AC, Robison LL, Boice Jr JD. Female survivors of childhood cancer: preterm birth and low birth weight among their children. J Natl Cancer Inst. 2006;98:1453–61.
14. • Green DM, Nolan VG, Kawashima T, Stovall M, Donaldson SS, Srivastava D, Leisenring W, Robison LL, Sklar CA. Decreased fertility among female childhood cancer survivors who received 22–27 Gy hypothalamic/pituitary irradiation: a report from the Childhood Cancer Survivor Study. Fertil Steril. 2011;95:1922–7, 1927.e1.

This important research presents data demonstrating that even very low levels of irradiation to the pituitary may impair fertility in females.

15. Familiari G, Caggiati A, Nottola SA, Ermini M, Di Benedetto MR, Motta PM. Ultrastructure of human ovarian primordial follicles after combination chemotherapy for Hodgkin's disease. Hum Reprod. 1993;8:2080–7.
16. van Beek RD, van den Heuvel-Eibrink MM, Laven JS, de Jong FH, Themmen AP, Hakvoort-Cammel FG, van den Bos C, van den Berg H, Pieters R. de Muinck Keizer-Schrama SM. Anti-Mullerian hormone is a sensitive serum marker for gonadal function in women treated for Hodgkin's lymphoma during childhood. J Clin Endocrinol Metab. 2007;92:3869–74.
17. Wallace WH. Oncofertility and preservation of reproductive capacity in children and young adults. Cancer. 2011;117:2301–10.
18. Jadoul P, Anckaert E, Dewandeleer A, Steffens M, Dolmans MM, Vermylen C, Smitz J, Donnez J, Maiter D. Clinical and biologic evaluation of ovarian function in women treated by bone marrow transplan-

tation for various indications during childhood or adolescence. Fertil Steril. 2011;96:126–133.e3.

19. Thibaud E, Rodriguez-Macias K, Trivin C, Esperou H, Michon J, Brauner R. Ovarian function after bone marrow transplantation during childhood. Bone Marrow Transplant. 1998;21:287–90.
20. Sanders JE. Growth and development after hematopoietic cell transplant in children. Bone Marrow Transplant. 2008;41:223–7.
21. Sanders JE, Hawley J, Levy W, Gooley T, Buckner CD, Deeg HJ, Doney K, Storb R, Sullivan K, Witherspoon R, Appelbaum FR. Pregnancies following high-dose cyclophosphamide with or without high-dose busulfan or total-body irradiation and bone marrow transplantation. Blood. 1996;87:3045–52.
22. Ash P. The influence of radiation on fertility in man. Br J Radiol. 1980;53:271–8.
23. Sklar CA, Robison LL, Nesbit ME, Sather HN, Meadows AT, Ortega JA, Kim TH, Hammond GD. Effects of radiation on testicular function in long-term survivors of childhood acute lymphoblastic leukemia: a report from the Children Cancer Study Group. J Clin Oncol. 1990;8:1981–7.
24.•• Green DM, Kawashima T, Stovall M, Leisenring W, Sklar CA, Mertens AC, Donaldson SS, Byrne J, Robison LL. Fertility of male survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Clin Oncol. 2010;28:332–9.

This study from the CCSS cohort presents excellent epidemiologic data on the relative risk of males siring offspring after receiving cancer therapy in childhood. The data examined included all doses and volumes of radiation therapy received and all chemotherapeutic agents including cumulative doses of alkylating agents.

25. Hansen PV, Hansen SW. Gonadal function in men with testicular germ cell cancer: the influence of cisplatin-based chemotherapy. Eur Urol. 1993;23:153–6.
26. Howell SJ, Shalet SM. Spermatogenesis after cancer treatment: damage and recovery. J Natl Cancer Inst Monogr. 2005;34:12–7.
27. Anserini P, Chiodi S, Spinelli S, Costa M, Conte N, Copello F, Bacigalupo A. Semen analysis following allogeneic bone marrow transplantation. Additional data for evidence-based counselling. Bone Marrow Transplant. 2002;30:447–51.
28. Quinn GP, Vadaparampil ST, Lee JH, Jacobsen PB, Bepler G, Lancaster J, Keefe DL, Albrecht TL. Physician referral for fertility preservation in oncology patients: a national study of practice behaviors. J Clin Oncol. 2009;27:5952–7.
29. Letourneau JM, Ebbel EE, Katz PP, Katz A, Ai WZ, Chien AJ, Melisko ME, Cedars MI, Rosen MP. Pretreatment fertility counseling and fertility preservation improve quality of life in reproductive age women with cancer. Cancer. 2011.
30. Janson C, Leisenring W, Cox C, Termuhlen AM, Mertens AC, Whitton JA, Goodman P, Zeltzer L, Robison LL, Krull KR, Kadan-Lottick NS. Predictors of marriage and divorce in adult survivors of childhood cancers: a report from the Childhood Cancer Survivor Study. Cancer Epidemiol Biomarkers Prev. 2009;18:2626–35.
31. Ethics Committee of the American Society for Reproductive Medicine. Fertility preservation and reproduction in cancer patients. Fertil Steril. 2005;83:1622–8.
32. Lee SJ, Schover LR, Partridge AH, Patrizio P, Wallace WH, Hagerty K, Beck LN, Brennan LV, Oktay K. American Society of Clinical Oncology. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol. 2006;24:2917–31.
33. Lobo RA. Potential options for preservation of fertility in women. N Engl J Med. 2005;353:64–73.
34. Ginsburg ES, Yanushpolsky EH, Jackson KV. In vitro fertilization for cancer patients and survivors. Fertil Steril. 2001;75:705–10.
35. Noyes N, Porcu E, Borini A. Over 900 oocyte cryopreservation babies born with no apparent increase in congenital anomalies. Reprod Biomed Online. 2009;18:769–76.
36. Rudick B, Opper N, Paulson R, Bendikson K, Chung K. The status of oocyte cryopreservation in the United States. Fertil Steril. 2010;94:2642–6.
37. Cobo A, Meseguer M, Remohi J, Pellicer A. Use of cryo-banked oocytes in an ovum donation programme: a prospective, randomized, controlled, clinical trial. Hum Reprod. 2010;25:2239–46.
38. Donnez J, Silber S, Andersen CY, Demeestere I, Piver P, Meirow D, Pellicer A, Dolmans MM. Children born after autotransplantation of cryopreserved ovarian tissue. a review of 13 live births. Ann Med. 2011;43:437–50.
39. Ting AY, Yeoman RR, Lawson MS, Zelinski MB. In vitro development of secondary follicles from cryopreserved rhesus macaque ovarian tissue after slow-rate freeze or vitrification. Hum Reprod. 2011;26:2461–72.
40. Xu M, Barrett SL, West-Farrell E, Kondapalli LA, Kiesewetter SE, Shea LD, Woodruff TK. In vitro grown human ovarian follicles from cancer patients support oocyte growth. Hum Reprod. 2009;24:2531–40.
41.• Dolmans MM, Marinescu C, Saussoy P, Van Langendonckt A, Amorim C, Donnez J. Reimplantation of cryopreserved ovarian tissue from patients with acute lymphoblastic leukemia is potentially unsafe. Blood. 2010;116:2908–14.

Demonstrated that reimplanted ovarian tissue from patients with hematologic malignancies may potentially lead to reseeding a cancer recurrence.

42. Morice P, Juncker L, Rey A, El-Hassan J, Haie-Meder C, Castaigne D. Ovarian transposition for patients with cervical carcinoma treated by radiosurgical combination. Fertil Steril. 2000;74:743–8.

43. Chen H, Li J, Cui T, Hu L. Adjuvant gonadotropin-releasing hormone analogues for the prevention of chemotherapy induced premature ovarian failure in premenopausal women. Cochrane Database Syst Rev. 2011;11:CD008018.
44. Piccioni P, Scirpa P, D'Emilio I, Sora F, Scarciglia M, Laurenti L, De Matteis S, Sica S, Leone G, Chiusolo P. Hormonal replacement therapy after stem cell transplantation. Maturitas. 2004;49:327–33.
45. Castelo-Branco C, Rovira M, Pons F, Duran M, Sierra J, Vives A, Balasch J, Fortuny A, Vanrell J. The effect of hormone replacement therapy on bone mass in patients with ovarian failure due to bone marrow transplantation. Maturitas. 1996;23:307–12.
46. Schmiegelow ML, Sommer P, Carlsen E, Sonksen JO, Schmiegelow K, Muller JR. Penile vibratory stimulation and electroejaculation before anticancer therapy in two pubertal boys. J Pediatr Hematol Oncol. 1998;20:429–30.
47. Nicopoullos JD, Gilling-Smith C, Almeida PA, Ramsay JW. The results of 154 ICSI cycles using surgically retrieved sperm from azoospermic men. Hum Reprod. 2004;19:579–85.
48. Levron J, Madgar I, Shefi S, Meirow D, Wiser A, Bider D, Dor J, Raviv G. IVF outcome with cryopreserved testicular sperm. Andrologia. 2011;43:48–51.
49. Ginsberg JP, Carlson CA, Lin K, Hobbie WL, Wigo E, Wu X, Brinster RL, Kolon TF. An experimental protocol for fertility preservation in prepubertal boys recently diagnosed with cancer: a report of acceptability and safety. Hum Reprod. 2010;25:37–41.