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Reproductive Health and Cancer in Adolescents and Young Adults

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Reproductive Health and Cancer in Adolescents and Young Adults

Foreword by Brad Zebrack

Springer

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Foreword

Last year marked two major milestones in my life. I turned 50 years old, and I have lived half my life – 25 years – as a cancer survivor.

The invitation to write the forward to this important text on reproductive health for young adults with cancer offered me an opportunity to reflect on my own daughter's birth and my path to parenthood nine years ago.

I recall the day when my wife Joanne and I decided to leave the house for the first time since our daughter Sierra's birth. Living in a self-contained nest, we finally needed food and supplies, and mostly just wanted to get out of the house. So we began to prepare. What might we need when taking a 6-day old infant out into the world? Diaper bag, with all the accoutrements – changing board, spare diapers, wipes. Oh, a bottle in case she gets hungry. Carrier. Stroller. The baby, of course. Oh, maybe we should feed her before we go. Done. OK, now check diaper. Oops! Diaper change. Now dress her. What should she wear on a hot August afternoon in Los Angeles? Redress her. Then dress her back into the first outfit. Find a hat. Blanket?

An hour and a half later we were ready to head to Target. And too tired to go. So we said "forget it; maybe tomorrow."

Fast forward to yesterday. Almost nine years later. Sierra's school is holding its end-of-year Ice Cream Social and street dance. Hundreds of grade school kids and parents are out in the yard, celebrating the anticipation of summer vacation. The once helpless and vulnerable infant who we could not get out of the house on the 6th day of her life is now a thriving 3rd grader, dancing in the street and laughing with her friends. She is beautiful.

These are some of the anxieties and joys of parenthood that I never would have known that I was missing had I not had a child. Yet there was a time when, after unsuccessful attempts at artificial insemination and costly in vitro fertilization, my wife Joanne and I resigned ourselves to a life without children of our own. We each had brothers and sisters with children, and decided that we would play active roles in the lives of our nieces and nephews.

Meanwhile, instead of raising a family during our late 20s and 30s, Joanne and I did a lot together. We hiked and biked and backpacked and travelled. We packed up and moved from California to Michigan for graduate school, then re-packed and returned to California five years later. We got "real" jobs, with benefits! We bought a house. We did what many others our age were doing, except of course raising children. We turned 40 years old. Life was good.

But coming home from work one night and sitting down to dinner, we asked ourselves: Is this all there is? After deciding we would be childless and

that we were okay with that decision, we changed our minds. It was time to consider adoption.

Two and half years later, we were at the bedside as our daughter Sierra Grace was born, and thus began the memories and challenges and joys of parenthood that I ***now*** know and cherish.

I have been a cancer patient but also a clinician who has helped patients and family members deal with the multiple and various challenges that occur throughout phases of cancer diagnosis, treatment, and transitions to off-treatment survival or the end of life. As a researcher and advocate whose work focuses on the quality of life for cancer survivors and their loved ones I feel that this text is an invaluable educational resource that targets unique needs and issues faced by young adults fighting cancer during their reproductive years. The authors provide an excellent review of the impact of cancer on reproductive health and options for maintaining reproductive health throughout a continuum of care. They also address issues and challenges related to family building and parenthood. Most importantly, this book highlights salient challenges, questions, and emotions for clinicians and researchers to consider when working with the young adult cancer population.

Brad Zebrack

Acknowledgements

Writing a book is a lot like having a baby. It begins with the conception of an idea, some hard labor, and the nurturing of the product of that labor for many years to come. Although there are many ways to have a baby or parent a child, there is one constant across them all – it is not done alone. In that regard, we must acknowledge the many individuals who helped bring this book into the world. Starting with Ilse Henson, publishing assistant who saw promise in the idea of a book about reproductive health and cancer and encouraged us to pursue it, created the path for it to happen, and navigated us through the process. Next we had the good fortune of working with authors who were willing to spend long hours drafting chapters, responding to edits, and editing yet again with each step of the review process. We are indebted to this group of skilled experts who shared their knowledge and years of clinical and research experiences in these chapters. We like to think of this group as encompassing the "good genes" that gave rise to the birth of this book. As with a traditional pregnancy, a steady diet of continuous attention, regular appointments, and watching for warning signs are keys to a healthy baby. The constant attention, interest and good work of the following people contributed to the success of this book: Michele Griffin, Alison Nelson, Bethanne Bower, Devin Murphy, and Nicole Hutchins. The extended family of this book, our own families, also donated their efforts by supplying continuous encouragement – we'd like to thank Amanda, Caity, Abby, Blake, Tim, Lisa, Robert, Jennifer, Matt, Joey, Jacob, Maya, Sam, Ali, and Rajesh. Their presence in our lives has allowed us to understand and appreciate the importance of ensuring that all individuals have the opportunity to build families based on their own future desires. We also thank Moffitt Cancer Center for providing the environment and resources to conduct our research. Finally, we are highly appreciative of the cancer survivors who allowed us into their lives by sharing their stories presented in the vignettes that begin each chapter. Your courage and honesty helped to shine a light on the great need for attention to reproductive health issues in the oncology world. We hope we have honored your struggles by creating this book.

This book is intended for current and future health care professionals and researchers who work with adolescent and young adult populations affected by or at risk for cancer. While there are varying definitions of the age range of this population, our goal was to focus on those of "childbearing potential", which typically begins at puberty and extends through the mid-forties. We

acknowledge that in this day of reproductive technologies, there are many men, and some women, who become parents beyond this age range. The attention to the broader aspect of reproductive health, outside of childbearing, doesn't begin or end at any age.

Introduction

There are an estimated 70,000 new cancers diagnosed each year among men and women between the age of 15 and 39 and 143,000 in ages 40–45. Recognizing the unique clinical, psychosocial, and quality of life impacts cancer may have based on an earlier than average age of diagnosis, these individuals are often categorized as the Adolescent/Young Adult (AYA) population. The chapters in our text focus either on AYA as a whole or in a few chapters on certain segments of AYA such as pediatric cancer patients or adolescents, or parents of young children.

Infertility and reproductive health issues are an expected consequence of most cancer treatments that include chemotherapy and/or radiotherapy. Although fertility may be regained after some cancer treatments, sustained infertility develops in 50–95% of cancer survivors. Rates of cancer-related infertility in men and women vary and depend on a number of factors, including age, sex, diagnosis, treatment dose/intensity, size/location of radiation field, and the patient's pretreatment fertility status. Women have a 40–80% chance of losing fertility following chemotherapy or radiation during reproductive years and 30–75% of male cancer patients become sterile after cancer treatment. Given the improvements in cancer treatment and survival as well as advances in reproductive medicine that have occurred over the past several decades, the unique reproductive health needs of this group must be considered – beginning at initial diagnosis and continuing through to survivorship care.

There are fertility preservation options available prior to initiation of cancer treatment for AYA populations to assist in preserving or maintaining fertility such as sperm banking, oocyte and embryo cryopreservation and testicular and ovarian tissue freezing. Conversely, reproductive health particularly as it relates to pregnancy and sexually transmitted infection risks are an important consideration. For some cancer patients, there may be a perception that there is little risk of pregnancy due to the cancer treatments and therefore they engage in risky sexual behavior (e.g., unprotected sexual intercourse). The use of contraception for the prevention of pregnancy during treatment is an essential component of quality care. Furthermore, females with certain hormone dependent cancers must consider the type and duration of contraception in relation to their cancer type. Less is known about the need for contraception to prevent a partner from exposure to chemo or radiation during or after treatment.

For patients currently pregnant or who become pregnant after a cancer diagnosis, there are numerous medical and psychosocial considerations. While many survivors' may have healthy pregnancies and offspring, health care professionals and researchers must be aware of the pharmacokinetics of chemotherapeutic agents during pregnancy and lactation, and the effects on placenta, fetus and infant as well as recognizing that additional psychological support may be required in the unique clinical situation of cancer in pregnancy and personalized counseling for contraceptive use during and after treatment. For individuals at high risk of familial cancers, prenatal diagnosis and preimplantation genetic diagnosis should be offered after appropriate genetic consultation and counseling in a regional genetic service.

Early and ongoing consideration about a patient's current and future family building plans and desires is also of critical importance. For those patients who have already experienced loss of fertility through the cancer and/or the associated treatment, counseling about additional family building options such a donor sperm, embryos, gestational carriers, or adoption is warranted. Additionally, for patients who are already parents, there is a tremendous need for support and resources to assist in managing the psychosocial and emotional needs of their children.

The concerns of young cancer survivors in relation to the interplay of body image, relationships, fear of recurrence, and sexuality are often a source of great anxiety which can significantly impact quality of life. New research is aiding in the design of interventions and programs to help AYA survivors prepare for quality survival in relation to the psychosocial "late effects" which may be experienced in ways not seen in the traditional population of older adult cancer survivors.

Despite evidence that patients want information about future fertility, existing research finds large gaps between recommended and actual clinical practice related to discussion of fertility preservation options with cancer patients. There are many barriers at the provider, institutional and policy level that may impact communication and discussion related to fertility preservation and reproductive health issues.

Finally, despite advances in cancer treatment and options to preserve fertility have greatly advanced in the past decade, there are still many considerations related to the ethical and legal issues surrounding these issues such as the disposition of stored gametes and consideration of posthumous reproduction.

Contents

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Principles of Cancer Treatment: Impact on Reproduction

1

Kenny A. Rodriguez-Wallberg, MD, PhD

A lot of advances have been made in science, technology and reproduction but still we can't say for sure who will or will not be temporarily or permanently sterile from cancer or the treatment. So I think it's best to discuss it will all patients who are of reproductive age. It's not an easy discussion to have. You've just told someone they have cancer and now you tell them they may not be able to have kids. Some people don't care, or at least they think they don't care at the time. Some people are more upset about the news of infertility than they are about the cancer. You can't assume because you look at a patients chart that you know how they feel about fertility. Even if they already have kids or they aren't married or they are struggling financially, it's something that has to be discussed.

I had a testicular cancer patient, Sam, a few years ago with late stage disease. When I talked to him about fertility he got very excited – he said it was the most hopeful thing he'd heard since he came to the hospital. Then I wondered if I had given him false hope, because his odds were not too good, In fact they were pretty dismal. But that guy was bouncing off the wall with joy at the thought of banking sperm, and I thought maybe he would benefit from thinking some happy thoughts for a while. He did bank sperm, and it seemed to lift his spirits but in the end, he didn't survive the cancer.

I had a female patient with a GU cancer who said she wanted no part of a discussion about preserving fertility. She was only 25, but she said she knew she didn't want kids, and had never wanted them. So I stopped trying to talk about it. She did well and she's in graduate school now and just got married. At her last check-up, she told me she wished she had listened to me about the fertility. Now that she's doing well and married she has a new perspective on children and just learned she is infertile. She and her husband are trying to adopt but it's not an easy process for a cancer survivor. That taught me a lesson. I now insist my patients listen to the infertility talk, even if they say they don't want kids I try to explain that a lot of people feel differently when the treatment is over and they go on with their lives. I even tell them about Sam and how much hope that sperm banking gave him in his last days. I think as oncologist we have to not only talk about how to manage the disease, but how to prepare for survivorship. Sometimes we have to talk about end-of-life issues too. None of it is easy, but it's all worth it.
Dr. A, Oncologist

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Introduction

According to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database [1], 1,445,000 new cases of invasive cancer (766,860 in men and 678,060 in women) were diagnosed in the US in 2007

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[1]. Approximately 1,530,000 new cancer cases were expected to be diagnosed in 2010 (789,620 in men and 739,940 in women). Men have an overall 45% risk of developing cancer at some time during their lives, which is higher than in women who present with 37% lifetime cancer risk. Age is the most significant risk factor for cancer in both sexes. However, even younger adults and children may develop cancer, and in people younger than 39 years, the risk is of about 1/72 for men and 1/51 for women. For adults between 40 and 59 years, 1/12 men and 1/11 women will develop cancer.

With modern cancer treatment, nearly two thirds of patients diagnosed with cancer can get cured today. Cancer treatment in young adults and children may have detrimental effects on the reproductive system and negatively affect the quality of life of cancer survivors [2, 3].

As shown in Table 1.1, the most common cancer in females is breast cancer, followed by cancers of the digestive and respiratory systems and genital organs, in particular uterus, ovary and cervix. In males, the most common cancers arise in the genital organs prostate and testicle, followed by cancers of the digestive, respiratory and urinary systems and skin. Haematologycal malignancies and lymphoma are also common cancers in both sexes, particularly presenting at young ages [1].

Table 1.1 Cancer incidence in both sexes expected for year 2010 in the US

Primary site	Estimated new cancer cases for females	Estimated new cancer cases for males
All sites	739,940	789,620
Breast	207,090	1,970
Digestive system	125,790	148,540
Colon	53,430	49,470
Rectum	17,050	22,620
Liver & bile duct	6,690	17,430
Esophagus	3,510	13,130
Stomach	8,270	12,730
Pancreas	21,770	21,370
Respiratory system	110,010	130,600
Lung and bronchus	105,770	116,750
Genital organs	83,750	227,460
Endometrium	43,470	
Ovary	21,880	
Cervix	12,200	
Prostate		217,730
Testis		8,480
Urinary system	41,640	89,620
Urinary bladder	17,770	52,760
Kidney and renal pelvis	22,870	35,370
Endocrine system	35,040	11,890
Thyroid	33,930	10,740
Lymphoma	33,980	40,050
Skin	31,400	42,610
Melanoma	29,260	38,870
Leukemia	18,360	24,690
Myeloma	9,010	11,170
Brain and other nervous	10,040	11,980
Oral cavity and pharynx	11,120	25,420

Adapted from: Cancer Facts & Figures – 2010, American Cancer Society (ACS), Atlanta, Georgia, 2010
Incidence projections are based on rates from the North American Association of Central Cancer Registries (NAACCR) from 1995 to 2006, representing about 89% of the US population
SEER Cancer Statistics Review 1975–2007, National Cancer Institute, updated January 7, 2011 [1]

Principles of Cancer Treatment

Cancer treatment techniques include surgery, radiation therapy, chemotherapy, hormone therapy (in case of hormone sensitive tumors), and biological therapy (including immunotherapy and gene therapy). Surgery and radiation therapy are considered local treatments and chemotherapy and biological therapy are systemic. Hormone therapy is systemic and targeted to specific hormone receptors.

Surgery may impact fertility by removing reproductive organs or damaging structures needed for reproduction. Chemotherapy and radiotherapy have a known toxic effect on the gonads, ovaries, and testicles, and may induce gonadal failure. The impact of biological therapy on reproduction is largely unknown.

Cancer Surgery

Surgery is the most effective cancer treatment today. Eventually 40–100% of patients may be cured with the highest success when complete removal of the tumor is obtained. Surgery may be also indicated for cancer prophylaxis, such as the case of premalignant disease of the cervix in female patients. In very early stages of cervix cancer, the surgical excision of a significant part of the cervix, known as conization or even a small loop excision, may afford to patients a complete disease-free survival. Surgery of the cervix may induce subfertility by affecting the normal functioning of the cervix and its glandular secretion. These iatrogenically-induced cervical causes of infertility may be treated with success with intrauterine insemination and more advanced techniques of assisted reproduction as In Vitro Fertilization (IVF).

Whenever the complete removal of the tumor aiming to a curative treatment may not be obtained, reduction of tumor size by surgery may improve patient's chances to cure by facilitating the response to adjuvant chemotherapy or radiotherapy in the treatment of cancer tumors.

Surgery may also affect future fertility if there is removal or damage of the reproductive organs. In male patients, surgery for pelvic cancer such as for prostate, bladder or colon cancer may damage nerves and affecting potency or ejaculation. Surgical adjuvant treatment by removing the gonads may be indicated in female and male patients with hormone sensitive tumors.

In case of large tumors, chemotherapy and radiation may be indicated as first line treatment aiming to a reduction of tumor size and control of subclinical metastatic disease before surgical treatment. This is known as neo-adjuvant therapy. Thereafter, surgical treatment is planned to remove residual tumor masses. Neo-adjuvant therapy is usually planned before surgery in female patients with stage III breast cancer and young male cancer patients with bulky testicular cancer.

There has been a gradual development in gynecologic oncologic surgery and urologic oncologic surgery, aiming at preserving reproductive organs in female and male patients, respectively, without compromising survival. Fertility-sparing surgery is an option today for selected patients. The indication for such interventions often includes a well differentiated low-grade tumor in its early stages or with low malignant potential. The surgical fertility-sparing approaches available for women are shown in Table 1.2 [4].

The most established fertility preservation procedure for women in this group is the radical trachelectomy, offered to women with early stage cervical cancer. The surgery aims at removing completely the cervix tumor while preserving the uterus. Although conservative surgery offers the opportunity to preserve the reproductive organs, it offers no guarantee of achieving pregnancy or live-birth. Causes of subfertility may be present in the patients either due to pre-existing conditions or following the surgical treatment (i.e., scar formation) and a number of those patients may further require assisted reproduction treatments. In cases of selected ovarian tumors (i.e. borderline tumors) young female patients may be offered a single oophorectomy aiming at preserving the uterus and the contralateral ovary for future reproduction, (Table 1.2) [4].

In men, testicular cancer is the most prevalent cancer, and it presents often at a young age when fertility concerns may be an issue. For selected patients, unilateral and partial orchidectomies have developed as conservative cancer treatments aiming at preserving hormonal and sperm production and, thus, fertility potential. Experience with this method was first obtained in the treatment of pre-pubertal patients with benign teratomas [5]. The German Testicular Cancer Study Group reported a 98.6% disease-free survival rate at a follow-up of 7 years after conservative surgery of tumors <2 cm with negative biopsy findings of the tumor bed [6].

Radiotherapy in Cancer Treatment

It is known that cancer cells present with defects in their ability to repair sub-lethal DNA, whereas normal cells have the ability to recover. High dose

Table 1.2 Fertility-sparing interventions in female patients (with permission from Rodriguez-Macias Wallberg and colleagues [4])

Diagnosis	Type of surgery	Description	Obstetric outcome	Oncologic outcome
Cervical cancer stage IA1,1A2,1B1	Radical vaginal trachelectomy	Laparoscopic pelvic lymphadenectomy. Vaginal resection of the cervix and surrounding parametria keeping the corpus of the uterus and the ovaries intact	Spontaneous pregnancies described in up to 70%. Risk of second trimester pregnancy loss and preterm delivery	Rates of recurrence and mortality are comparable to those described for similar cases treated by means of radical hysterectomy or radiation therapy
Borderline ovarian tumors FIGO stage I	Unilateral oophorectomy	Removal of the affected ovary only, keeping in place the unaffected one and the uterus	Pregnancies have been reported and favorable obstetric outcome	Oncologic outcome is comparable with the more radical approach of removing both ovaries and the uterus. Recurrence 0–20% vs 12–58% when only cystectomy was performed
Ovarian epithelial cancer stage I, grade 1	Unilateral oophorectomy	Removal of the affected ovary only, keeping in place the unaffected one and the uterus	Pregnancies have been reported and favorable obstetric outcome	7% recurrence of the ovarian malignancy and 5% deaths
Malignant ovarian germ cell tumors/sex cord stromal tumors	Unilateral oophorectomy	Removal of the affected ovary only	Pregnancies have been reported and favorable obstetric outcome	Risk of recurrence similar to historical controls
Endometrial adenocarcinoma Grade 1, stage 1A (without myometrial or cervical invasion)	Hormonal treatment with progestational agents for 6 months	Follow-up with endometrial biopsies every 3 months	Pregnancies have been reported	Recurrence rate 30–40%. Five percent recurrence during progesterone treatment

ionizing radiation is a physical form of cancer treatment that aims at damaging cancer cells by breaking DNA through generation of free radicals from cell water. Damage of cell organelles and membranes kills cancer cells. Radiation therapy is, however, applied locally and although cancer cells are the target, radiation may also induce damage to normal cells in the tissues.

The response to radiation therapy depends on various factors such as the phase of cell cycle the cells are (cells in late G1 and S are more resistant), the degree of cell ability to repair the DNA damage and other factors such as hypoxia (hypoxic cells are more resistant), tumor mass, and growth fraction. Non-dividing cells are more resistant than dividing cells.

Radiation therapy can be administered as teletherapy, which aims at treating a large volume of tissue. For small volumes of tissue, such as in the case of cervix cancer in the female, radiation therapy can be administered in encapsulated sources of radiation that can be implanted directly into or adjacent to tumor tissue. Radiation therapy is a component of curative therapy for a number of diseases, including breast cancer, Hodgkin's disease, head and neck cancer, prostate cancer, and gynecologic cancers.

Effects of Radiotherapy on Reproduction

The male testis, female ovary, and bone marrow are the most sensitive organs to radiation therapy. The extent of the damage in females and males depends on the dose, fractionation schedule, and irradiation field [7, 8]. Whenever female reproductive organs are involved in the irradiated field, i.e., the ovaries, the uterus and the vagina may be compromised and damaged by direct irradiation. There is also evidence of damage of these organs by scattered radiation. In the female, radiation therapy results in dose-related damage of the gonads by the reduction in the nonrenewable primordial follicle pool. In women, the degree and persistence of the damage is also influenced by age at the time of exposure to radiotherapy due to a greater reserve of primordial follicles in younger women [9]. Table 1.3 presents a compilation of current knowledge on the impact of radiation doses in gonadal function of women and men [10]. In female and male pediatric patients, failure in pubertal development may be the first sign of gonadal failure.

Table 1.3 Radiation therapy protocols with high or intermediate impact on ovarian and testicular function (Adapted from reference [Rodriguez-Wallberg and Oktay, 10] with permission)

High risk of prolonged azoospermia in males or amenorrhea in females
Total Body Irradiation (TBI) for bone marrow transplant/stem cell transplant
Testicular radiation dose > 2.5 Gy in adult men
Testicular radiation dose ≥ 6 Gy in pre-pubertal boys
Pelvic or whole abdominal radiation dose ≥ 6 Gy in adult women
Pelvic or whole abdominal radiation dose ≥ 10 Gy in post-pubertal girls
Pelvic radiation or whole abdominal dose ≥ 15 Gy in pre-pubertal girls
Intermediate risk
Testicular radiation dose 1–6 Gy from scattered pelvic or abdominal radiation
Pelvic or whole abdominal radiation dose 5–10 Gy in post-pubertal girls
Pelvic or whole abdominal radiation dose 10–15 Gy in pre-pubertal girls
Craniospinal radiotherapy dose ≥ 25 Gy

In men, radiation therapy damages the gonadal stem cells and the spermatogoniae, which are responsible for the continual differentiation and production of mature spermatozoa. By contrast, the Leydig cells, responsible for the hormonal production of testosterone are more resistant to radiotherapy. However, it is known that Leydig cells of prepubertal boys, which are responsible for the hormonal production of testosterone, have a greater sensitivity to high doses of radiation therapy than those of older males [11]. If Leydig cell function remains after radiation therapy in childhood, patients may present with normal pubertal development in some cases. However, many of those patients will present at adulthood with reduced testicular size, impaired spermatogenesis and infertility, although with well preserved sexual function in most cases.

In adult women and prepubertal girls, use of shielding to reduce scatter radiation to the reproductive organs when possible is the standard medical procedure currently offered to preserve fertility. When shielding of the gonadal area is not possible, the surgical fixation of the ovaries far from the radiation field known as oophoropexy (ovarian transposition) may be considered. It is estimated that this procedure significantly reduces the risk of ovarian failure by about 50% and that those patients may retain some menstrual function and fertility [12]. Scattered radiation and damage of the blood vessels that supply the ovaries are related to the failure of this procedure [12].

Radiotherapy of the uterus in young women and girls has shown to induce tissue fibrosis, restricted uterine capacity, restricted blood flow, and impaired uterine growth during pregnancy, as shown by follow-up of cancer survivors [13, 14]. The uterine damage seems to be more pronounced in the youngest patients at the time of radiotherapy. As a consequence, radiotherapy-treated female patients present with a high risk of unfavorable pregnancy outcomes, such as spontaneous abortion, premature labor, and low birth weight offspring [13, 14].

Irradiation of the vagina is related to fertility and sexual issues due to loss of lubrication, anatomical impairments, and, in some cases, stenosis.

In males, use of shielding to reduce the dose of radiation delivered to the testes when possible is also recommended, and, in most centers, is a standard measure offered currently to adult patients and children.

Total body irradiation (TBI) given in conjunction with myeloablative conditioning prior to bone marrow transplantation is one of the most toxic treatments for the gonads, and is highly related to gonadal failure in both sexes [15, 16].

Cranial Irradiation and Hormonal Dysfunction

Disruption of the hypothalamic-pituitary-gonadal axis is a recognized potential complication of cranial irradiation that can lead to infertility in female and male patients. Follow-up of female patients treated post- and pre-pubertally with cranial irradiation for primary brain tumors has shown a high incidence of primary hypothalamic dysfunction as well as pituitary dysfunction with gonadotropin secretion disturbances. In some cases, precocious puberty may also be induced by cranial irradiation in childhood, which has been attributed to cortical disruption and disinhibition of the hypothalamus.

Chemotherapy

Chemotherapy given as only treatment may be curative for a series of cancer presenting in young adults and children.

Knowledge of the risk of gonadal damage caused by cancer treatment is essential to recognize patients at risk of gonadal failure. Table 1.4 summarizes the gonadotoxic impact of chemotherapy agents on the female ovary and male testis. In a vast majority of cancer treatments, chemotherapy combines several agents and there is a possibility of a synergistic gonadotoxic effect when several agents are given combined, although at lower doses particularly when combining alkylating drugs [16]. In the female, the primordial oocytes, which constitute the female follicle pool, are nonrenewable and reduce through apoptotic loss throughout the female life span, until complete depletion during menopause. Women's undeveloped oocytes and pregranulosa cells of primordial follicles are particularly sensitive to alkylating agents by induced apoptosis, which has been demonstrated in vitro and in vivo when human ovarian tissue has been xenotransplanted in SCID mouse [17, 18]. Ovarian failure is thus common after alkylating treatment [10].

Because of a reduction of the primordial follicle pool with ageing, older women have a higher risk of developing ovarian failure and permanent infertility after a cancer treatment when compared with younger women [8]. Younger patients at the time of cancer treatment may have a higher chance of recovering ovarian function following chemotherapy, and they should be recommended

Table 1.4 Gonadotoxic impact of chemotherapeutic agents in the female ovary and male testis

High risk of prolonged azoospermia in men or amenorrhea in women
Cyclophosphamide
Ifosfamide
Melphalan
Busulfan
Nitrogen mustard
Procarbazine
Chlorambucil
Intermediate risk
Cisplatin with low cumulative dose
Carboplatin with low cumulative dose
Adriamycin
Low risk
Treatment protocols for Hodgkin lymphoma without alkylating agents
Bleomycin
Actinomycin D
Vincristine
Methotrexate
5-fluorouracil

not to delay childbearing for too many years [4]. Although the absence of menstrual cycles, known as amenorrhea, should be considered unfavorable as it may be due to permanent gonadal failure, the presence of cycles should not be interpreted as proof of fertility. In the clinical setting, the gynecological examination by ultrasound, including estimation of small ovarian follicles of approximately 2–7 mm (antral follicle counts, AFC), and the determination of hormones, such as follicle-stimulating hormone (FSH), inhibin, and anti-mullerian hormone (AMH), may help the clinician in evaluating patient's remaining ovarian reserve after a cancer treatment and counseling on her chances to obtain a pregnancy.

Patients should be advised to avoid conception in the 6–12 month period immediately following completion of treatment due to toxicity of cancer treatments on growing oocytes [17]. This is owing to the higher risk of teratogenesis during or immediately following chemotherapy. Recent data support the return of DNA integrity over time after a cancer treatment and most studies conducted in cancer survivors have not shown any significant increase of fetal anomalies in infants that are conceived later [19, 20].

In male patients, prepubertal status does not provide protection from gonadal damage when alkilating agents are given at high doses. Because most chemotherapy agents are given as part of a combination regimen, it has been difficult to quantify the gonadotoxicity of individual drugs [21].

Conclusion

Because of progress in cancer therapy, long-term survival is expected for most of young adults and children of both sexes diagnosed with cancer today. Infertility, as a consequence of cancer treatment, has a recognized negative impact on quality of life of cancer survivors and, therefore, effects of modern cancer therapy on reproductive potential need to be discussed. This chapter outlines general principles of cancer treatment and the impact of the cancer surgery, radiation therapy, and chemotherapy on reproduction.

Provider Recommendations

1. Surgery for cancer is the most effective treatment. Improvements in gynecologic and urologic surgery have improved in the ability to preserve fertility, but some patients may require surgeries that impair fertility.
2. Surgical adjuvant treatment of gonad removal may be indicated in male and female patients with hormone sensitive tumors.
3. Radiotherapy can damage normal tissue cells and may impair male or female fertility by causing damage to reproductive organs. In females, damage to uterine function from radiation may impact ability to maintain a pregnancy.
4. Radiation to the brain can impair fertility by impacting hypothalamic pituitary functioning.
5. Chemotherapy can damage oocytes and sperm as well as the functioning.
6. Patients are advised to avoid conception for at least six months post-chemotherapy treatment.
7. Discussing fertility preservation options with all patients of childbearing age is suggested.

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