New Jersey Commission on Cancer Research

A SPECIAL REPORT OF THE

NEW JERSEY COMMISSION ON CANCER RESEARCH

IN COLLABORATION WITH THE

NEW JERSEY PEDIATRIC HEMATOLOGY ONCOLOGY NETWORK *(NJPHON)*

N J P H O N

AN UPDATE FOR PRIMARY CARE PHYSICIANS

Fall 2002

MANAGING ADULT SURVIVORS OF CHILDHOOD CANCER FERTILITY AND SEXUAL FUNCTIONING

INTRODUCTION

In the past two decades, survivorship from pediatric cancers has soared, and it is estimated that in 2010 one in 250 young people will be a survivor of a childhood cancer[i]. Studies indicate that many of these individuals are at risk of infertility, gonadal dysfunction and both physical and psychosocial difficulties with aspects of sexuality. As a consequence of the changing referral patterns necessitated by managed care, primary care practitioners will be presented with an increasing population of adults who are long term survivors of cancer and who will require some special attention to these issues.

While a large percentage of survivors of childhood cancers do retain their reproductive and sexual functioning, for some, infertility and impaired sexual functioning is "adding insult to injury." When young adults are surveyed, it is diminished or compromised fertility, premature menopause and issues related to sexuality that rank high on the list of concerns with which they grapple.[ii] For these reasons, primary care physicians may play a key role in identifying, assessing and referring patients at risk for reproductive or sexual problems.

It is important to note that when fertility is achieved, progeny of cancer survivors without inherited conditions are not at increased risk of malignancy or congenital defects. **However, identifying survivors at especially high risk for infertility and psychosocial sequelae and referring them to appropriate specialists is essential.** Assisted reproductive techniques have improved the outlook for fertility, but there may be a limited window of opportunity for the cancer survivor to successfully conceive and bear children.

CHALLENGES TO FERTILITY, REPRODUCTIVE AND SEXUAL FUNCTIONING

The risk of impaired functioning varies considerably by a number of factors, including gender, age, diagnosis and treatment modality.

Some of these factors include:

GENDER

For females, risks of childhood cancer treatment may include some of the following:[iii]

- Surgical removal, or chemical destruction of ovarian function
- Delayed or arrested puberty
- Hormonal deficits
- Infertility
- Premature menopause
- Increased incidence of miscarriage
- Premature or low birth-weight babies
- Small uterus with decreased elasticity
- Dyspareunia (hormonal and/or due to fibrosis)
- Physical or psychological constraints on sexual functioning
- Altered body image, feelings of worthlessness, or fears of rejection

For males the risks can include:

- Surgical interventions which remove essential reproductive organs
- Delayed or arrested puberty
- Hormonal deficits
- Erectile dysfunction (hormonal and/or vascular)
- Absent or low sperm count
- Physical or psychological constraints on sexual functioning
- Lack of experience with sexuality appropriate to the age, and altered self-image as a result of disease site or treatment

For females, the potential for reproductive dysfunction is increased by the fact that the same insult will affect both oocyte *and* hormonal production, as these are linked. For males, sperm production and hormonal production are not linked, so some aspects can survive when others are impacted. Gender differences are also noted relative to specific treatment modalities.

AGE

Age at diagnosis and treatment can play a significant role in the level of risk for reproductive dysfunction. This risk is disproportionate among young females and males.

- As a general rule, pre-pubertal gonads are more resistant to therapy effects, but they are not immune.
- Treatment received in adolescence generally has more impact on fertility than when the treatment is administered to young children.
- Treatment at a younger age generally imposes fewer risks to the reproductive system than those experienced by older adolescents, unless they were less than six years of age with a cancer of the CNS or leukemia requiring cranial radiation.
- There are some specific exceptions related to treatments described below.

Young adult cancer survivors often present as especially mature, as the disease experience may generate such a response, but many still feel socially and sexually inadequate. Excessive dependence on, or overprotection by, parents for an extended period may prevent development of autonomy as an essential developmental milestone.

DIAGNOSIS

It is important to know the specific diagnosis, as it provides clues to the treatment modalities, dose intensity of chemotherapy or radiation, (if administered) and the extent to which vital reproductive organs were affected. In cases of Hodgkins disease below the diaphragm, sarcoma involving the abdomen and/or pelvis and advanced stage Wilms' tumor, therapy is likely to have included radiation that may threaten gonadal and/or reproductive function.

TREATMENT MODALITY

ALKYLATING AGENTS

Alkylating agents are the main chemotherapeutic offenders in producing fertility and reproductive dysfunction (See Table I.) The ovaries appear to be more resistant than the testes to the impact of these agents, although this is not an absolute. High intensity and/or cumulative doses of alkylating agents can be a factor in premature menopause.

Absolute gonadotoxic doses of alkylating agents are not known. However it is suspected that total cumulative dose (TCD) of cyclophosphamide greater than 7.5 gm/m² can begin to increase risks of infertility. Concern is increased if TCD is greater than 10 gm/m².

TABLE I. ALKYLATING AGENTS

Busulfan	Melphalan	Cyclophosphamide (CYX)
CCNU	BCNU	Cisplatinum
Carboplatinum	DTIC	Ifosfamide
Mechlorethamine	Procarbazine	

RADIATION THERAPY

Consistent with effects described above, treatment at a younger age generally imposes fewer risks to the reproductive system than those experienced by older adolescents. However, when radiation therapy is administered at an older age, females experience more damage than males. RT exposure to the abdomen, pelvis, brain, spine, hip or femur, or total body irradiation (TBI) all put survivors at risk of gonadal sequelae.

- For women under age 40, more than 2,000 cGy of radiation to the gonads causes complete ovarian failure. Treatment for diagnoses that require whole abdomen RT may also predispose females to ovarian failure.
- RT below the diaphragm may contribute to premature menopause.
- The growing uterus is especially vulnerable to RT.
- For males, RT in excess of 600 cGy may kill all sperm stem cells.
- Most males also experience failure of Leydig cell function with prepubertal RT doses in excess of 2,000 cGy; 3,000 cGy for adolescents and young adults.

BONE MARROW TRANSPLANT

Bone Marrow Transplant (BMT) with dose intensive chemotherapy, especially with TBI, has an adverse affect on fertility and gonadal function. It has been estimated that 100% of female BMTx recipients will develop ovarian failure if older than 10 years of age when transplanted. In one study, 92% of males and 99% of females developed gonadal dysfunction after BMTx.[iv]

COMBINATION THERAPIES

Not surprisingly, combination therapies increase the risks to the young cancer survivor. In one study, treatment of females after puberty with RT below the diaphragm and exposure to alkylating agents increased the risk of premature menopause by more than two fold. Any female with one or more of these risk factors, who is complaining of new onset menstrual irregularities, vaginal dryness or hot flashes should be evaluated for premature menopause.

INTERVENTIONS

It is essential to obtain a summary that includes age at diagnosis and treatment, all treatment modalities, doses of chemotherapy and RT and any complications. Pediatric cancer survivors often lack even a basic knowledge of their diagnosis, treatments or anticipated outcomes. If they were quite young, details of their diagnosis and treatment parameters might not have been shared; older adolescents are often "spared the details" of their disease.

Raising issues of fertility and sexuality is often difficult for both patient and physician. An open, non-judgmental attitude is essential. It is important to review the potential for premature menopause, infertility and sexual problems with the patient so that a program of surveillance and intervention can be designed to address these concerns. Often, very targeted questions are necessary to elicit deeply held concerns, especially about sexual functioning and altered self-image which may result from cancer treatment.

Impaired, painful or difficult sexual functioning may be due to the effects of treatment on gonadal/endocrine function, or may be the result of the patient's lack of knowledge. Sexual attitudes and behavior are learned in childhood, and young cancer survivors may have missed many opportunities to gain information and experience. Physical and pharmaceutical aides to sexual functioning may be appropriate.

Immediate assessment is important. This is not a subject to defer until symptoms arise. Often the effects of the treatment do not become apparent until adolescence or young adulthood. Because some survivors may face a very limited window of opportunity for fertility, exploring the patient's interest in childbearing, and related concerns must be addressed initially.[v] The prospects of premature menopause should be considered.

A comprehensive evaluation of the fertility status of young women should include:

- Pubertal staging – to identify any delay
- Menstrual history (amenorrhea)
- Presence of current symptoms of premature menopause: decline of ovarian function, vaginal dryness, decrease in estrogen production
- Signs of elevated level of follicle stimulating hormone (FSH)
- Evidence of elevated level of luteinizing hormone (LH)
- Presence of decreased level of estrogen

Assessment of the fertility status of young men should include analysis of:

- Pubertal staging – to identify delay
- Elevated FSH
- Small testicular size for age
- Evidence of elevated LH
- Signs of decreased testosterone
- Sperm analysis, an essential element for diagnosis, is the only reliable parameter of fertility in the male.

Impressive technological advances are now available to assist in achieving both fertility and satisfying sexual functioning. Patients should be encouraged to be open to all possibilities and guided in the exploration of all options. When it is possible, timely and appropriate referral to a reproductive endocrinologist (for females), infertility urologist (for males), and/or an accredited sex therapist, is important**.**

Specific and unique surveillance may be required for the survivor of pediatric cancer.

- If the patient has premature menopause, surveillance for bone mineral density is necessary.
- If a female had RT to the pelvis or required hormonal treatment during times of uterine growth, even with natural or assisted conception the uterus may not have normal size or elasticity to support pregnancy to term, and may require special, high risk monitoring.
- Treatment with some chemotherapy agents, such as anthracyclines, nitrosoureas, high dose cyclophosphamide and/or bleomycin may increase cardiac and pulmonary function problems during pregnancy and should be monitored.
- Females on early hormone replacement therapy (HRT), because of primary amenorrhea or premature menopause, must be carefully monitored and continually re-evaluated given that the risks of long-term usage are not fully known.

Sexuality encompasses much more than intercourse; it includes feelings of attractiveness to others, maintaining personal relationships, the ability to become excited, and the physiological need for effective lubrication in preparation for sexual activity. Patients should be encouraged to seek both medical advice and psychosocial counseling, and/or to participate in appropriate support groups when they express these concerns. Groups can provide for role playing, peer feedback and group validation for the "normalcy" of the individuals concerns.[vi]

This Update is the outcome of a consensus multidisciplinary round table of leading experts in reproductive endocrinology, urology, internal medicine, psychosocial oncology and oncology

A number of resources are available to you and your patients for further information on these issues:

The National Cancer Institute maintains web sites for both professionals and for patients. They can be accessed through: www.nci.nih.gov or by 1-800-4-Cancer
The American Cancer Society can be accessed through www.cancer.org or 1-800-ACS-2345

Guest Editor: Beverly Ryan, MD, Director, Cure and Beyond, Tomorrows Children's Institute at Hackensack University Medical Center

Editorial Services Provided by: Denyse L. Adler, MA, The Adler Group, Montville, NJ

Panel Members:

Javier Aisenberg, MD, Pediatric Endocrinology
Hackensack University Medical Center
Donna Astiz, MD, Department of Medicine
Morristown Memorial Hospital
Jeanne Carter, PhD, Psychiatry
Memorial Sloan Kettering Cancer Center
Alice Cohen, MD, Adult Oncology
SBHCS at Newark Beth Israel Medical Center
Alice Ettinger, RN, Pediatric Oncology Nursing
Saint Peter's University Hospital
Maragret Garrisi, Fertility & Reproductive Medicine
Saint Barnabas Medical Center
Darleen Gibbons, MD, Gynocologic Oncology
The Cancer Institute of New Jersey
Allison Grann, MD, Radiation Oncology
Saint Barnabas Medical Center
Michael B. Harris, MD, Pediatric Oncology
Tomorrows Children's Institute at Hackensack
University Medical Center
Libby Klein, LCSW, Social Worker
Tomorrows Children's Institute at Hackensack
University Medical Center
Susan Murphy, MD, Pediatric Oncology
Saint Barnabas Medical Center
Barbara Rabinowitz, PhD, Psychology of Human Sexuality
The Medical Center of Ocean
Beverly Ryan, MD, Pediatric Oncology
Tomorrows Children's Institute at Hackensack
University Medical Center
Eric Seaman, MD, Male Infertility & Reproductive
Medicine, Morristown Urology Associates
Paulette Stanford, MD, Development of Adolescents
UMDNJ-New Jersey Medical School

The New Jersey Commission on Cancer Research
The NJCCR is a state agency created to support and promote cancer research in New Jersey through competitive grants, fellowships and educational programs. Comments, questions and other information about this newsletter may be obtained by calling NJCCR offices at (609) 633-6552

New Jersey Pediatric Hematology Oncology Network
NJPHON serves as an advisory group to the New Jersey Commission on Cancer Research and provides an umbrella organization promoting collaboration among the ten pediatric cancer centers serving children with cancer in New Jersey.

---

[i] "Outlook: Life Beyond Childhood Cancer, University of Wisconsin System, www.outlook.life.org, 2000
[ii] Schneider D, Huang J, Palanisamy K, "Focus Group Study to Determine Issues for Long-term Childhood Cancer Survivors." New Jersey Pediatric Hematology/Oncology Network. Poster for *Cancer Survivorship Throughout the Lifespan: Challenges for the 21st Century*. Atlantic City, NJ. October 2000.
[iii] Schover L, "Psychosocial aspects of infertility and decisions about reproduction in young cancer survivors: A review," Medical and Pediatric Oncology 33:53-59, 1999
[iv] Mertens et al, Bone Marrow Transplantation, 22:345-350. 1998
[v] Chiarelli A, Marret L, Darlington G, "Early menopause and infertility in females after treatment for childhood cancer diagnosed in 1964-1988 in Ontario, Canada," Am J Epidemiol, 150:3, 245-254, 1999
[v] Schover L, 1999
[vv] Sklar C, "Reproductive physiology and treatment-related loss of sex hormone production," Medical and Pediatric Oncology 33:2-8, 1999
[v] Schover L, 1999
[v] Woolverton K, Ostroff J, "Psychosexual Adjustment in Adolescent Cancer Survivors," Cancer Investigation 18(1), 51-58 2000
[v]Ibid
[v] Ibid
[vi] Ibid

State of New Jersey
Commission on Cancer Research
28 West State Street
PO Box 360
Trenton, NJ 08625-0360

FIRST CLASS MAIL
U.S. POSTAGE
PAID
TRENTON, NJ
Permit No. 21