Preserving Fertility After Cancer

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ABSTRACT In this review, the reproductive impact of treatments for several common cancers and options to maintain fertility in women and men undergoing treatment for these cancers will be discussed. The options available to any particular cancer survivor will depend on her or his age at the time of diagnosis and treatment, cancer type and primary site, stage, and type of treatment. (CA Cancer J Clin 2005;55:211–228.) © American Cancer Society, Inc., 2005.

INTRODUCTION

In the past, the primary goal of cancer therapy—survival—tended to overshadow survivorship considerations. However, with recent advances in oncology, survival rates are increasing, and therefore, issues affecting long-term cancer survivors become more important and more widely recognized. Preserving fertility is an important issue for cancer survivors. Over the past 20 years in the United States, there have been statistically significant increases in the 5-year survival rates for most cancers.1 Cancer survivors can often be offered the possibility of preservation of ovarian function and future fertility without compromising treatment outcomes or their survival.2 Surgical, medical, and technological advances have enabled the medical community to provide fertility options for patients with cancer. Treating oncologists need to consider fertility options in patients undergoing therapy. The ability of having genetically related children is an important issue for patients surviving cancer.

In this review, the options to maintain fertility in women and men undergoing treatment for cancer will be discussed. The options available to any particular cancer survivor will depend on the age of the patients at the time of diagnosis and treatment, cancer type, severity and location, and type of treatment.

OVARY ANATOMY AND PHYSIOLOGY

The outer cortex of the ovary contains the oocytes and is the site of hormone production. The peak number of oocytes, approximately $6.8 \times 10^6$, occurs at 5 months gestation, after which there is no further proliferation of germ cells. This store decreases to $2 \times 10^6$ at birth, with 300,000 left at puberty. A typical woman will ovulate 300 to 500 mature eggs during her reproductive life span, while the rest of the follicles become atretic.3 It is this nonrenewable nature that makes oocytes so susceptible to damage.4 The first phase of oocyte maturation starts in utero, occurs continuously, and is gonadotropin-independent. At puberty, a gonadotropin-dependent phase begins where follicles are primed by follicle-stimulating hormone, resulting in granulosa cell proliferation. Luteinizing hormone triggers ovulation with the potential for fertilization.3

EFFECTS OF RADIATION AND CHEMOTHERAPY ON THE OVARY

Radiation

Damage induced by radiation or chemotherapy is progressive and irreversible in the ovary, resulting in amenorrhea and infertility.5,6 Gosden demonstrated depletion of primordial follicles in mouse ovaries in a dose-related fashion using increasing radiation doses of 0.1, 0.2, and 0.3 Gy. This explains premature ovarian failure with exposure to lower doses of radiation, while total depletion of follicular reserve occurs at higher doses.7 The likelihood of
permanent ovarian failure following radiation increases with advancing age. Women over 40 years of age have a smaller pool of remaining oocytes and require only 5 to 6 Gy to produce permanent ovarian failure, while 20 Gy are needed to produce permanent ovarian failure in women less than 40 (Table 1).8,9 Although younger women (< age 35) tend to have resumption of normal menses, they still remain at risk for infertility and premature menopause. Dose- and distribution-dependent relationships also exist. Treatment doses of 20 to 35 Gy result in a 22% infertility rate, while doses of >35 Gy result in a 32% infertility rate.

Total-body irradiation (TBI), as used before stem cell transplantation, is associated with greater than 90% permanent gonadal failure in women overall, and an incidence of pregnancy less than 3%.10 The outlook for recovery of ovarian function among women who received TBI before puberty is more favorable, particularly if the radiation was delivered in several fractions.10

Although pregnancy is possible following pelvic radiation, a long-term sequela of radiation is its effect on the uterus and on subsequent pregnancy outcomes. Uterine radiation is associated with infertility, spontaneous pregnancy loss, and intrauterine growth retardation.11 Direct effects on the uterus after abdominal radiation in young girls being treated for childhood cancers have included irreversible changes in uterine musculature and blood flow.12 Significantly decreased uterine volume (up to 40% of normal adult size), which is unresponsive to hormone therapy, has been observed in girls who received abdominal radiation. In addition, no increase in the endometrial stripe was observed in those who also received hormone replacement during their radiation.12,13 Doppler flow was also decreased among patients who received radiation, suggesting damage to the vasculature.13,14 Theoretically, these changes could lead to inadequate placentation, a process that depends on adequate blood and hormonal support.12 Even those who received TBI, which involves exposure to lower doses of pelvic radiation, experience these same effects on the uterus.14 In addition, these effects on the uterus have been implicated in the observed obstetrical complications seen in patients who received radiation. Spontaneous abortions occur at a rate of 38% compared with 12% in the general population, preterm labor 62% compared with 9%, and low birth weight infants 62% compared with 6%.12–16 However, there is no increased risk of subsequent teratogenicity as long as radiation is not administered during a pregnancy.8,13,14,27–30

### Chemotherapy

Rates of amenorrhea following chemotherapy vary based on the age of the patient, duration of chemotherapy, and dose of chemotherapy delivered.17 Toxicity can occur through impairment of follicular maturation and/or depletion of primordial follicles.18,19 Older age, higher doses, and longer duration all increase the toxic effects of chemotherapy on the ovary. With the same chemotherapeutic regimen (cyclophosphamide, methotrexate, and fluorouracil [CMF]), rates of amenorrhea are 35% to 40% in women less than 40 years of age compared with 80% to 95% in women over 40 years of age.19,61

Significant toxicity has been attributed specifically to alkylating agents, which act on undeveloped oocytes and possibly pregranulosa cells of primordial follicles and do not require

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**Table 1: Radiotherapy-induced Damage to the Reproductive Tract**

| Sex      | Site                      | Effect                                  |
|----------|---------------------------|-----------------------------------------|
| Males    | Cranial/TBI*              | Endocrine axis disruption                |
|          | TBI/pelvic/testes         | Germinal epithelium                     |
|          |                           | >1.2 Gy - azoospermia                   |
|          |                           | 0.1–1.1 Gy - oligospermia               |
|          |                           | Leydig cells                            |
|          |                           | >20 Gy - prepubertal                    |
|          |                           | >30 Gy - post-pubertal                  |
|          |                           | Endocrine axis disruption               |
| Females  | Cranial/TBITBI/           | Ovarian failure (LD<sub>50</sub> < 4 Gy) |
|          | abdomen/pelvic            | Older women > 5 Gy                      |
|          |                           | Younger women > 20 Gy                   |
|          |                           | Uterine damage                          |
|          |                           | Decreased volume                        |
|          |                           | Decreased elasticity                    |

*TBI, total body irradiation.

Adapted from Thomson AB, Critchley HO, Kelnar CJ, Wallace WHB with permission from Elsevier.9
cell proliferation for their cytotoxic action (Table 2). Byrne and colleagues reported that significantly increased relative risks of menopause during the early 20s occurred after treatment with either radiotherapy alone (relative risk, 3.7) or alkylating agent alone (relative risk, 9.2). They also found that 42% of women treated with chemotherapy, some of whom resumed normal menses, reported premature menopause by the age of 31, compared with 5% of the population controls. Based on these observations, most clinicians advise their patients not to wait more than a few years after treatment to try and conceive, as long as the patients do not have oncologic contraindications to pregnancy. However, there are no data to support these empiric recommendations.

Chemotherapy regimens used as conditioning for stem cells transplantation are, like TBI for the same indication, highly gonadotoxic. Recovery of ovarian function is rare following regimens that include busulphan and cyclophosphamide, whereas melphalan-based regimens show less reproductive toxicity. To reduce the cytotoxic effects of radiation and chemotherapy, some investigators have attempted to render the germinal epithelium quiescent by creating an artificial prepubescent state using a gonadotropin-releasing hormone (GnRH) agonist. GnRH agonists act on the hypothalamic–pituitary axis to suppress ovarian function. While Agca and colleagues were successful in decreasing cyclophosphamide-induced toxicity in rats and rhesus monkeys, the same success has not been consistently achieved in humans. Meirow and colleagues demonstrated no protective effect of GnRH after ablative chemotherapy and radiotherapy in patients undergoing bone marrow transplant. In 2002, Blumenfeld reported that 94% of patients who received a GnRH agonist with cyclophosphamide resumed normal ovulatory menses, and only 6% experienced permanent ovarian failure. In contrast, in the patients who did not receive a GnRH agonist with chemotherapy, less than one half resumed normal ovulatory menses, and 56% experienced permanent ovarian failure. However, this study was small (<100 patients) and was not double-blinded or randomized, which introduces patient and investigator bias. In addition, both groups contained patients who also received radiation, although the authors do not describe in detail. This group of patients received conventional chemotherapy as contrasted with the series of patients described in the Meirow report. Other small studies in premenopausal patients with breast cancer have demonstrated that it is well tolerated and may protect long-term ovarian function. Larger randomized studies are needed.

The oral contraceptive pill has also been investigated as an agent to suppress the ovaries during chemotherapy and invoke protection from these cytotoxic agents. In a small study, Chapman and colleagues reported more follicles on ovarian biopsies in three patients receiving combination oral contraceptive pills during chemotherapy than those who did not receive oral contraceptive pills. Whitehead et al. found no protective effect from combination oral contraceptive pills in patients who received chemotherapy for Hodgkin disease. In a retrospective study, they found of 44 women treated, 9 took oral contraceptive pills during their treatment. Four of nine patients (44%) were amenorrheic after completion of treatment, three patients (33%) were oligomenorrheic, and two patients (22%) had resumed normal menses. These results were similar to the group as a whole, as 17 patients (39%) were amenorrheic, 10 patients (22%) were oligo-

| TABLE 2 Gonadotoxic Chemotherapy Agents in Male and Female Patients |
|---------------------------------------------------------------|
| **Alkylating agents**                                         |
| Cyclophosphamide                                             |
| Ifosfamide                                                   |
| Nitrosoureas (eg BCNU, CCNU)                                 |
| Chlorambucil                                                 |
| Melphalan                                                    |
| Busulphan                                                    |
| Vinca alkaloids                                              |
| Vinblastine                                                  |
| Antimetabolites                                              |
| Cytarabine                                                   |
| Platinum agents                                              |
| Cisplatinum                                                  |
| Others                                                       |
| Procarbazine                                                 |

Adapted from Thomson AB, Critchley HO, Kelnar CJ, Wallace WHB with permission from Elsevier.
menorrheic, and 17 patients (39%) had resumed normal menses.26

Although there is ovarian damage from chemotherapy, there seems to be no risk of toxicity to future offspring of women treated with these agents before pregnancy.27–30,55 Most chemotherapeutic drugs are excreted in the urine within a few days. Teratogenic risk exists if pregnancy occurs immediately following or during chemotherapy treatment for some drugs administered in the first trimester. There are no increases in congenital malformations or rates of preterm labor in pregnancies following chemotherapy. However, these observations are based on small studies, and the length of follow up has been limited. Based on animal data, a minimum of 6 months is recommended between chemotherapy completion and pregnancy.

OVARIAN CRYOPRESERVATION:
AN EMERGING TECHNOLOGY

Risk of ovarian damage persisting after treatment for malignancies has prompted the medical community to provide young women desiring future fertility alternative options to maintain their reproductive potential before chemotherapy. In vitro fertilization (IVF) with frozen embryos has an approximately 20.4% success rate for pregnancy per cycle, with limitations.31 Many young women with gynecologic cancer do not have a partner to provide sperm at the time of diagnosis. Use of donor sperm is possible in such a case but may not be an ideal option for some women. Often cancer treatment cannot be delayed for the IVF process, which can take up to 6 to 8 weeks. Lastly, there are concerns with ovarian stimulation in patients with estrogen-sensitive tumors.

Freezing oocytes has had some success, but with significant limitations and only a small number of reported pregnancies.110 Metaphase II oocytes do not tolerate cycles of freeze-thaw well, which can result in aneuploid conceptuses.7 Attempts to freeze an immature egg with in vitro maturation and fertilization have also proven technically challenging.3 Overall, current survival rates of the oocyte for the freeze-thaw process range from 15% to 43% with approximately 45% fertilization rates but only 1% to 2% clinical pregnancy rates.15,32–34 Survival of the oocyte after thawing is not necessarily a guarantee of unaltered viability with successful fertilization, pregnancy, and viable delivery.

These limitations have spurred researchers to evaluate cryopreservation of ovarian cortical strips. The technique is easy, fast, and inexpensive. In this technique, 3,500 primordial follicles are obtained from 5 to 6 laparoscopic ovarian biopsies. These immature oocytes are more quiescent and smaller than mature oocytes, making them far more tolerant to freezing and thawing injuries.3 Hundreds of immature oocytes are cryopreserved without the necessity of ovarian stimulation and subsequent delay of cancer treatment. Following treatment for the malignancies, these primordial follicles require maturation in vitro, as orthotopic or heterotopic autografts, or as xenografts in severe combined immunodeficient (SCID) mice. Autologous orthotopic transplantation involves reimplanting the thawed ovarian tissue back into its anatomic pelvic location, allowing for the possibility of natural fertilization. Disadvantages include possible difficulty monitoring the follicles with ultrasound should assisted reproductive technology be necessary, a second surgery to replace the tissue, and most importantly, the possibility of reimplanting microscopic cancer. Oktay has transplanted ovarian cortical strips to the forearm, with publication of data from two patients, with no pregnancies to date.35 Heterotopic xenograft transplantation to immune deficient mice with IVF and embryo transfer is even more experimental. Oktay and his group have demonstrated follicle maturation to antral-secretory stages and corpus luteum formation in SCID mice.3,35,36 The major disadvantage is concern about transferring animal pathogens to humans. In addition, longevity of the transplants is unknown. Success rates as defined by pregnancies are currently poor, with only one reported pregnancy resulting in a live birth reported to date from reimplantation of an
ovarian cortical strip. Other options are available including oocytes donation, surrogate pregnancy, and adoption.

**TESTICULAR ANATOMY AND PHYSIOLOGY**

In males, germinal stem cells are present from the time of birth but do not develop into the haploid gametes capable of fertilizing an oocyte (spermatogenesis) until the boy goes through puberty. Spermatogenesis is a process, beginning at puberty and continuing throughout life, whereby totipotential stem cell spermatogonia undergo continual self-renewal and differentiation into mature spermatozoa.9 In the relatively quiescent prepubertal testis, there is a steady turnover of early germ cells that undergo spontaneous degeneration before the haploid stage is reached; nevertheless, it is likely that it is this steady state that renders the prepubertal testis vulnerable to the deleterious impact of cytotoxic therapy.9 Male factor infertility from cancer surgery or radiotherapy can result from anatomic changes (eg, hypogastric plexus damage leading to retrograde ejaculation), primary or secondary hormonal imbalance, or damage or depletion of germinal stem cells or supporting cells. These changes can result in compromised sperm number, motility, morphology, or DNA integrity.

**EFFECTS OF RADIATION AND CHEMOTHERAPY ON THE TESTIS**

**Radiation**

The degree and permanency of radiotherapy-induced testicular damage depends on the treatment field, total dose, and fractionation schedule. Leydig cells are more resistant to damage from the radiotherapy than is the germinal epithelium, and progression through puberty with normal hormone levels is common despite severe impairment of spermatogenesis. Testicular radiation with doses >20 Gy is associated with Leydig cell dysfunction in prepubertal boys, while Leydig cell function is usually preserved up to 30 Gy in sexually mature males (Table 1). Testicular germ cell toxicity is dose related and influenced by fractionation, with radiation delivered in a single dose having less effect than fractionated regimens.38 Doses as low as 0.1 Gy may result in oligospermia, whereas azoospermia generally occurs in men who receive more than 1.5 Gy.38–40 Sperm counts are typically at their lowest 4 to 6 months after treatment is completed; return to pretreatment levels usually occurs in 10 to 24 months, with longer periods required for recovery after higher doses.41

TBI as a conditioning regimen for stem cell transplantation causes permanent gonadal failure in approximately 80% of men.10

**Chemotherapy**

Regimens including high doses of alkylating agents are the most gonadotoxic, with prolonged azoospermia in greater than 90% of men who receive the highest doses of cyclophosphamide, procarbazine, chlorambucil, and/or BCNU (Table 2). Platinum compounds can cause prolonged azoospermia in up to 50% of men. Regimens without high doses of alkylators or platinum compounds are unlikely to cause prolonged azoospermia.88 Conditioning regimens used for stem cell transplantation cause prolonged azoospermia in more than one half of survivors; a few percent have fathered children, although there is insufficient information on the intentions of these men regarding fatherhood to estimate their fertility.14,88

Chemotherapy appears to lower healthy sperm counts in cancer survivors, but after an adequate time off of therapy, small studies suggest DNA integrity of sperm is reestablished similar to age-matched controls.42,43 The amount of time from therapy has not been adequately quantified. Larger studies and longer follow up are needed. The extent of the damage is dependent on the agent administered and the doses received. Several studies have reported that most offspring of cancer survivors do not have any adverse effects from preconception exposure to therapy.27–30,55

**Sperm Cryopreservation**

For men, semen cryopreservation after masturbation is the preferred method of fertility
preservation. Other methods of semen collection are available (eg, penile vibratory stimulation and electroejaculation), particularly for younger adolescents. Limitations include suboptimal sperm quality even before cancer treatment, especially in testicular cancer, and the need to delay cancer therapy until several samples could be banked to ensure adequate and viable sperm. These limitations have been largely overcome by improvements in IVF technology. Intracytoplasmic sperm injection allows successful fertilization with a single sperm obtained from semen or by testicular sperm extraction.

Sperm cryopreservation in boys and young men includes all of these issues, as well as additional considerations. Spermarche is estimated to occur at approximately 13 to 14 years of age. If ejaculation is achieved, the patient’s age does not seem to affect the quality of sperm produced. However, statistics suggest that most men being treated for cancer do not participate in sperm banking and that most oncologists do not consistently discuss this option with their male patients at risk for treatment-related infertility. Most studies suggest that a minority (up to 30% but often less than 10%) of men return to use their stored specimens. Physicians must emphasize opportunities to preserve fertility before treatment. Psychological, logistical, and financial constraints for patients may further limit sperm banking options.

Hormonal therapy in men has generally not been successful in restoring or preserving fertility. Other methods, such as testicular tissue cryopreservation and reimplantation or maturational in SCID mice, remain investigational.

FERTILITY AND OUTCOMES AFTER THERAPY OF COMMON CANCER TYPES

The available evidence about the direct effect of prior cancer treatment on subsequent offspring is generally reassuring. The effect of radiation on the uterus and subsequent pregnancies has been described earlier in this review. Following completion of cancer therapy, rates of genetic malformations in offspring of pediatric cancer survivors exposed to potentially mutagenic treatments have been similar to other cancer survivors and sibling controls. However, most studies are small, and length of follow up has been limited. In aggregate, the data are reassuring.

The treatment of cancer during a pregnancy raises other issues. Potential problems include transplacental transfer of cancer, congenital malformations, gonadal dysfunction and infertility, poor physical, emotional, or neurologic development, or carcinogenesis in subsequent generations. Although limited by study design, publication bias, and small numbers, there does not appear to be a higher rate of perinatal problems as long as the well recognized teratogens are avoided during pregnancy.

The remainder of this review summarizes fertility strategies and outcomes for several common forms of cancer selected for inclusion based on a high prevalence of young adult and middle-aged survivors exposed to treatment modalities likely to adversely affect their fertility.

Breast Cancer

About 13% of all breast cancer diagnoses are in women younger than age 45, which translates to over 3,800 women per year in the United States alone. Most patients are treated with surgery, and many with chemotherapy and/or tamoxifen. Women who are treated with breast conserving surgery or have high risk of locoregional recurrence after mastectomy are also often treated with breast irradiation to decrease the risk of locoregional recurrence. The majority of women diagnosed with early-stage breast cancer have an excellent long-term prognosis, and many will undergo temporary or permanent cessation of menses with systemic therapy. This may be beneficial in terms of their breast cancer prognosis, especially if the breast cancer was hormone-receptor positive. However, many women are concerned about future infertility or the risk of developing symptoms or medical complications of early menopause following treatment. The risk of chemotherapy-related amenorrhea is related to patient age, the spe-
specific chemotherapeutic agents used, and the total dose administered.\textsuperscript{59,60} For example, 6 cycles of CMF are associated with 80\% to 95\% risk of amenorrhea in women over 40 compared with a 30\% to 40\% risk in women under 40.\textsuperscript{61} In comparison to CMF, doxorubicin and cyclophosphamide (AC) is associated with a lower incidence of amenorrhea in both older and younger women, likely because of the lower cumulative dose of cyclophosphamide with AC: 4 cycles of AC are associated with a 50\% to 60\% risk of amenorrhea in women over 40 compared with a 10\% to 15\% risk in women under 40.\textsuperscript{5} In women under the age of 30, premature ovarian failure, or menopause, with standard regimens is less common, although available studies are generally limited by the small number of women evaluated in this particular age group. With anthracycline-based adjuvant chemotherapy, at least two studies have found a 0\% incidence of amenorrhea in women under age 30.\textsuperscript{62–65} Rates of amenorrhea in women under age 30 following 6 cycles of CMF or CEF (cyclophosphamide, epirubicin, and 5-fluorouracil) are somewhat higher, up to 20\%.\textsuperscript{62–65} Despite the importance of this issue for many young women with breast cancer, many questions remain including the impact of treatment duration and dose density, as well as newer drugs (eg, the taxanes).\textsuperscript{66} In one small retrospective study, the addition of paclitaxel to AC did not appear to substantially increase the overall risk of chemotherapy-related amenorrhea\textsuperscript{67}; however, larger studies are needed to make more definitive conclusions.

Chemotherapy-related amenorrhea may be reversible; however, the vast majority of women who remain amenorrheic 1 year following treatment will not regain ovarian function. While endocrine therapies such as tamoxifen or ovarian suppression do not generally cause permanent cessation of menses, they involve years of treatment, during which time a pregnancy is contraindicated.\textsuperscript{65}

There are few data on actual fertility and pregnancy outcomes following chemotherapy in breast cancer survivors.\textsuperscript{68,69} Pregnancy in breast cancer survivors is complicated by a range of medical and psychosocial issues. Because breast cancer is responsive to various endocrine changes, there has been concern that continued menstrual cycling and/or pregnancy after breast cancer may worsen prognosis. To date, the effect of subsequent pregnancy after a diagnosis of breast cancer on prognosis including relapse and survival has not been studied prospectively.\textsuperscript{70} Evidence from retrospective studies on pregnancy following breast cancer has not shown an increased risk of recurrence or survival disadvantage; however, these studies are all limited by significant biases.\textsuperscript{71–85} Furthermore, information for women with breast cancer on assisted conception, including IVF before or following breast cancer treatment, is limited and mostly anecdotal.\textsuperscript{75} Until more definitive data are available, women and their physicians will continue to be concerned about the effects of a subsequent pregnancy on breast cancer prognosis. Conventionally, it is recommended that pregnancy be delayed until 2 to 3 years after completion of treatment. This is not because of evidence that there is no potential risk beyond 2 to 3 years, but so that women wait until the period associated with greatest risk of recurrence has passed before bearing children.\textsuperscript{70}

### Leukemia and Lymphoma

Approximately 22.6\% of leukemia diagnoses occur in individuals younger than 45 years. The corresponding numbers are 65.3\% and 15.8\%, respectively, for Hodgkin disease and non-Hodgkin lymphoma. Collectively, there are more than 13,400 people younger than 45 diagnosed with these 3 cancers in the United States each year.\textsuperscript{57}

The leukemias most common in this age group (eg, acute lymphoblastic leukemia and acute myeloid leukemia), Hodgkin disease, and non-Hodgkin lymphoma are typically treated with multiagent cyclic chemotherapy, which can cause temporary or permanent oligospermia or azoospermia in men and cessation of menses or premature ovarian failure in women. Lymphoma may also be treated with radiation therapy (up to 25–50 Gy) to sites of local disease that may encompass the ovaries and uterus, contributing to infertility. Cranial irradiation was used commonly...
in the past for acute lymphoblastic leukemia, although this treatment has been largely replaced in modern practice by intrathecal chemotherapy. In a Scandanavian cohort, female survivors of childhood acute lymphoblastic leukemia were as likely as the general female population to have given birth by age 23. However, the first birth rate was 61% lower for the subgroup whose treatment included cranial irradiation. No genetic diseases of childhood malignancies were reported among the children of male and female survivors in this series. A study of Children’s Cancer Group centers found that female acute lymphoblastic leukemia survivors were less likely than controls (their sisters) to have reported a pregnancy between age 18 and 21, but no difference was noted after age 21. Cranial radiotherapy substantially reduced the likelihood of pregnancy, particularly if it was delivered around the time of menarche; the relative fertility for this group was 27%. The overall fertility of male acute lymphoblastic leukemia survivors from the same cohort was not significantly different from that of sibling controls. However, in comparison with controls, the fertility rate for married survivors treated with cranial irradiation before age 10 was reduced by 91%.

Survivors of lymphoma (non-Hodgkin lymphoma and particularly Hodgkin lymphoma) have been among the most comprehensively studied with regard to fertility, because they tend to present at a young age and with a favorable prognosis. Although the diversity of tumor subtypes and chemotherapeutic regimens is substantial, there is a clear consensus that older regimens that include higher doses of alkylating agents (particularly procarbazine) such as mechlorethamine, vincristine, prednisone, and procarbazine or cyclophosphamide, vincristine, prednisone, and procarbazine cause more severe and prolonged reproductive toxicity to both women and men than do regimens such as doxorubicin, bleomycin, vinblastine, and dacarbazine; mitoxantrone, vincristine, vinblastine, and prednisone; or methotrexate, doxorubicin, vincristine, prednisone, and bleomycin. It is also clear that the likelihood of gonadal failure and infertility increases with the patient’s age at the time of treatment.

Previously discussed methods of fertility preservation apply to women with leukemia and lymphoma. Laparoscopic oophoropexy has been reported to be of benefit for women receiving pelvic nodal irradiation. However, this is a very small series. Oophoropexy in the past has only marginally prolonged ovarian function in studies with longer follow up. Although controversial, one observational study utilizing historical controls reported a lower rate (5% vs. 55%; \( P < 0.05 \)) of premature ovarian failure in women with lymphoma receiving GnRH agonists during chemotherapy.

Studies of ovarian tissue cryopreservation and reimplantation have included women with lymphoma. However, there remains a concern that hematogenously disseminated diseases such as leukemia and lymphoma could be reintroduced by ovarian tissue grafting. Available studies grafting human ovarian tissue into immunoincompetent mice both support and refute those concerns.

Successful pregnancies have been reported in women treated with chemotherapy or stem cell transplantation (autologous or allogeneic) for lymphoma and leukemia. Interestingly, an excess of twins is reported in women treated for Hodgkin disease who conceive naturally.

Likewise, the management for men with these neoplasms should focus on counseling and sperm cryopreservation interventions that are standard for a number of other tumor types. It appears that lower fertility of male Hodgkin disease survivors is due at least in part to the disease itself, rather than its treatment. Oligospermia and abnormalities of sperm structure/function are apparent in some of these patients even before treatment and are associated with advanced stage and elevated erythrocyte sedimentation rate.

Cervical Cancer

An estimated 43% of women with cervical cancer are diagnosed in their childbearing years, up to age 44, representing nearly 3,900 women annually in the United States. Forty-six percent of women with cervical cancer present with Stage I disease, which is usually curable by radiation and/or surgery. Most
women will have squamous cell carcinoma, and less commonly adenocarcinoma of the cervix. However, this distribution has been changing, particularly in young women. The Surveillance, Epidemiology, and End Results database reported a 107% increase in the proportion of adenocarcinomas relative to all cervical cancers between 1973 and 1996. The smaller the lesions, the more amenable they are to conservative therapies. Squamous cell carcinoma in situ and International Federation of Gynecologists and Obstetricians (FIGO) Stage IA1 invasive squamous cell cervical lesions (microscopic lesions with stromal invasion less than 3 mm in depth and less than 7 mm wide) can be managed by a cold knife cone biopsy. The pathology should be reviewed, and the margins of the cone biopsy need to be negative in patients with Stage IA1 lesions managed by cone biopsy as the definitive therapy. Although the rate of fertility is not compromised, the risk of spontaneous second trimester loss and premature delivery is higher, which is most likely related to the amount of cervical tissue resected.

Unlike squamous lesions, detection, diagnosis, and management of adenocarcinoma of the cervix are more complicated. Adenocarcinoma in situ (AIS) or “microinvasive” adenocarcinomas are lesions that may also be conservatively managed. The diagnosis of microinvasive adenocarcinoma is a pathologic challenge. These lesions (AIS and microinvasive adenocarcinomas) are usually multifocal and are generally located high in the endocervical canal. The traditional management is a hysterectomy. However, some studies have been done evaluating more conservative treatment options in highly motivated women desiring future fertility, with mixed results. Poynor et al. retrospectively evaluated their experience in the conservative management of AIS with disappointing results. Although they had a limited sample size (n = 28), their results challenged the previously held belief that margin status was a helpful predictor of recurrence and treatment success. Four of 10 (40%) patients with negative margins had a second surgical specimen containing AIS. In addition, positive margin status was associated with invasive adenocarcinoma in a second surgical specimen. Two patients had invasive cancer after a conization specimen revealed AIS only. Furthermore, 7 of 15 patients (47%) managed conservatively with either close follow up or repeat conization had a recurrence, 3 of whom had negative margins. Interestingly, not all patients with positive margins had a second surgery, either conization or hysterectomy. These findings are consistent with McHale, who found a 60% (3 of 5 patients with positive margins) recurrence rate with either adenocarcinoma or microinvasive adenocarcinoma after a cone biopsy for AIS.

In contrast, other authors have reported more promising results in their retrospective studies. Shin et al. reported a small series of patients with AIS. Of 132 patients identified as having AIS, 95 patients were conservatively managed with either a cold knife cone or loop electrosurgical excision procedure, and 37 underwent hysterectomy. Of those who underwent hysterectomy, margin status was a much more accurate predictor of residual disease: 13 of 21 (62%) with positive margins had residual disease in the hysterectomy specimen compared with only 1 of 16 (6%) who had negative margins. Patients with positive margins were offered repeat cone biopsies. Nine (38%) of the 24 patients who underwent repeat cone biopsies for positive margins had residual AIS, and no one had invasive adenocarcinoma. Twenty-three infants were delivered during the study period, one patient was pregnant at the time of publication, and three elected to terminate their pregnancies. Five patients had a miscarriage. Of those conservatively managed, nine women underwent repeat cone biopsies for abnormal follow up, three of whom had cervical intraepithelial neoplasia. There were no recurrences of AIS or invasive adenocarcinoma.

In general, the standard recommendation for women with AIS is hysterectomy, but cone biopsies can be done if the margins are negative and the patient fully understands the necessity as well as the challenges of follow up, specifically the difficulty of adequately sampling the endocervical canal. Further recommendations include consulting with a gynecologic oncologist.
gist and obtaining a review by another pathologist.

McHale had 20 patients with “early-invasive” adenocarcinoma, 4 of whom received a cone biopsy for treatment. There were no reported recurrences in these Stage IA1 patients, although all four had negative margins. Three had subsequent pregnancies with viable infants. Schorge et al. treated five women with Stage IA1 cervical adenocarcinoma with a cold knife cone biopsy. Three were Grade 1, one was Grade 2, and one was Grade 3. None had lymph-vascular space invasion, and all had negative margins on their specimen. None of the patients developed recurrent disease after 6 to 20 months of follow-up. Because of the small sample size, the safety of these conservative procedures in early invasive cancer cannot be adequately assessed. More studies need to be done to adequately address the conservative management of early adenocarcinoma of the cervix, including microinvasive disease. Conservative treatment for early invasive and microinvasive adenocarcinoma with cold knife cone biopsy should not be routinely performed.

Radical vaginal trachelectomy and pelvic lymphadenectomy is currently being investigated in the treatment of patients with FIGO Stage IA2 to IB invasive squamous cell carcinoma or adenocarcinoma of the cervix. Because Stage IA2 lesions carry a 5% risk of positive lymph nodes, a bilateral radical pelvic lymphadenectomy and selective para-aortic lymph node sampling is required. Thus, for Stage IA2 and IB, a laparoscopic lymphadenectomy is performed first, and if the nodes are negative for malignancy on frozen section, the trachelectomy portion is performed.

The trachelectomy specimen is sent for frozen section; a clear endocervical margin of 5 to 8 mm is required for adequate treatment, and at least 1 cm of endocervix is left for preservation of fertility. If adequate margins are achieved, a cerclage is placed. Dargent covers the cerclage with vaginal epithelium to avoid ascending infections (Saling procedure). Although this procedure is technically feasible, long-term follow up of adequate numbers of patients is needed to assess survival and pregnancy outcomes. Based on preliminary data from published studies, potential candidates include those who (1) desire future fertility; (2) are FIGO Stage IA1 (with lymphatic vessel invasion), IA2, and IB1 with a tumor size less than 2 cm; (3) have limited endocervical involvement (as assessed by magnetic resonance imaging); (4) and have no evidence of lymph node metastasis. Preferred characteristics include no infertility history, lack of capillary space involvement on cone biopsy, low grade histology, and squamous cell type. The studies to date have found an overall recurrence rate similar to radical hysterectomy (approximately 3%-4%), with estimated blood loss, rate of transfusion, hospital stay, and time to normal residual urine all decreased compared with radical hysterectomy. However, operating times were longer, and there were more intraoperative complications (mostly cystotomies), which were attributed to the learning curve for performing any new procedure. No ureteral injuries or trocar site recurrences were reported. Cesarean section is necessary for delivery, and patency of the cervical os is digitally restored at the time of cesarean.

Combining the published literature, out of a total 224 women, there were 96 pregnancies from 61 women, resulting in 51 live births (53% live birth rate), 35% of which were less than 34 weeks. In certain series, rates of preterm delivery were as high as 50%, mostly due to preterm premature rupture of membranes, believed to result from ascending infection. Reported obstetrical complications include mostly abortions, with 17% first trimester spontaneous abortions and 12.5% second trimester losses, which were attributed to a lack of cervical mucus, cervical incompetence, and increased subclinical chorioamnionitis. Because of these results, several authors recommend oral antibiotic therapy between 14 and 16 weeks to help eradicate vaginal flora, Gram stains to rule out bacterial vaginosis, covering the os with vaginal epithelium, and more frequent visits to detect cervical dilatation (bi-weekly from 18 to 28 weeks and weekly from 28 weeks until delivery). Dargent has had no cases of preterm delivery since he began the...
Saling procedure to avoid ascending infections. When cervical incompetence is diagnosed, another cerclage can be placed depending on the trimester. Finally, most studies recommend that the patient should wait 6 to 12 months after radical trachelectomy to attempt pregnancy.106 This procedure has begun to be performed in the United States. In 2003, Schlaerth et al.104 published their experience with this technique in 10 patients in the United States. Their findings were similar to that in Europe. Four pregnancies occurred: 2 losses at 24 and 26 weeks, 1 cesarean section at 32 weeks, and 1 cesarean section at 38 weeks. Two patients experienced cervical stenosis with hematometra, which required cervical dilatation for drainage. Based on this very small sample size, their recommendation was to avoid pregnancy for 1 year after treatment.104

Rodriguez et al.108 treated three patients with Stage IA1 and IA2 cervical cancer with abdominal radical trachelectomy and bilateral pelvic lymphadenectomy. An abdominal radical trachelectomy uses many techniques already familiar to gynecologic oncologists and achieves a wider parametrial resection than the vaginal approach, which is where two of the three patients in the Canadian report had their recurrence.107,108 All three patients in Rodriguez’ series were disease-free, and one was pregnant without assisted reproductive technology. No mention of attempts at pregnancy was noted in the other two patients.108

Although radical trachelectomy may provide young women an option of preserving her uterus for future childbearing, the procedure is still considered investigational. Larger, multicenter trials with longer follow up periods are necessary to truly assess the risk of recurrence and survival rates. Patients desiring this procedure should be referred to the centers performing this procedure. Based on the current literature, pregnancy should be delayed for 6 to 12 months following the procedure.

It is well established that conservation of the ovaries in early stage cervical cancer does not adversely affect survival, allowing these women to retain hormonal function by preserving oocytes, as well as potentially maintaining fertility potential.95,96 Ovarian transposition has been used to limit ovarian damage from radiation, a treatment option for patients with advanced cervical cancer.109 By creating a pedicle on the infundibulopelvic ligament and placing the ovary as high and lateral as possible in the paracolic gutters, it is believed that the dose of radiation exposure can be reduced to 10% of the administered dose. However, recent data reveal that patients who have had ovarian transposition have been shown to have a higher risk of premature menopause.5 Buekers111 reported that patients who underwent transposition without radiation experienced menopause 5 years earlier than the average. When transposition and radiation were combined, only 41% retained ovarian function and had a mean age of menopause 15 years below the average. The authors attributed these findings to vascular compromise leading to atresia, loss of function, and fibrosis.111

In addition to maintaining hormonal function, transposition is also performed to try and preserve future fertility. However, some authors have suggested that fertility is preserved in a mere 15% after ovarian transposition.5 Fujisawa112 transposed ovaries to the subcutaneous tissue where he found some evidence of ovarian function but was not able to isolate an egg for assisted reproductive technologies, therefore failing to achieve a pregnancy.5,112 Thus, transposition remains investigational at this time.

**Ovarian Cancer**

**Germ Cell Tumors**

Germ cell tumors account for 20% to 25% of all ovarian neoplasms, although only 2% to 3% are malignant.113 Malignant germ cell tumors are the principle type of ovarian cancer in women in their teens and early 20s. Dysgerminoma is the most common malignant germ cell tumor, two-thirds of which are diagnosed as Stage IA.114 The current standard for the treatment of all germ cell tumors, even in advanced stages, in women who wish to maintain fertility is a unilateral salpingo-oophorectomy and staging procedure consisting of an omentectomy, cytologic washings, peritoneal biopsies, and pelvic and para-aortic lymph node sampling.
The contralateral ovary is not biopsied unless grossly involved with tumor in an attempt to preserve future fertility by reducing the potential for adhesions. As these tumors are rarely bilateral, the patient is left with one ovary, one tube, and an intact uterus for future childbearing. Gershenson has reported that chemotherapy (bleomycin, etoposide, and platinum) is a very effective treatment for these tumors, with future fertility seemingly unaffected. Long-term follow up studies report normal ovarian function and successful pregnancies.

Tumors of Low Malignant Potential

Ovarian neoplasms of low malignant potential are epithelial ovarian tumors with histologic features of malignant tumors but without identifiable stromal invasion. They represent 10% to 15% of all ovarian cancers, with more than 50% occurring in women under the age of 40. Seventy percent are diagnosed as Stage I, with a 90% to 95% survival rate and 2.1% recurrence rate if diagnosed in this early stage. For all stages, the overall recurrence risk is 12% to 15%.

The standard treatment has been a unilateral salpingo-oophorectomy and staging procedure as described for germ cell tumors. Because these tumors occur in young women, the role of ovarian cystectomy (rather than unilateral salpingo-oophorectomy) has been explored. Data from a small number of cases indicate that the recurrence rate after a cystectomy (for all stages) is the same (12% to 15%) as after a unilateral salpingo-oophorectomy. However, Morice et al. found evidence to the contrary. In their experience, treating all stages, the recurrence rate was 36% (4 of 11 patients) after a cystectomy. In addition, 27% (12 of 44 patients) of patients treated conservatively (with adnexectomy, cystectomy, or both) had either Stage II or III disease, the largest number of patients treated conservatively reported in the literature. All recurrences were picked up during routine follow up, were noninvasive, and were successfully treated with surgery, in some cases with another cystectomy. Fourteen of the 44 patients treated conservatively were able to achieve a total of 17 pregnancies, 2 with assisted reproductive technology. Four achieved pregnancy after a repeat cystectomy for a tumor recurrence. Morice et al. concluded that the ideal treatment for low malignant potential tumors is unilateral salpingo-oophorectomy, with cystectomy reserved for those with a recurrent low malignant potential tumor, with a previous history of contralateral unilateral salpingo-oophorectomy and a strong desire to preserve future fertility.

A laparoscopic approach has been investigated by Seracchioli et al. The concerns for laparoscopy as the surgical procedure for epithelial ovarian cancer include tumor rupture and spillage, resulting in upstaging the patient and trocar implants. Seracchioli et al. conservatively treated 19 women for Stage I (A to C) low malignant potential tumors with a laparoscopic procedure, followed them with a second laparoscopic procedure at 6 to 12 months, and then followed them for a mean of 42 months. They reported one recurrence in a patient after a cystectomy, for which she received a second cystectomy. No patient received postoperative radiation or chemotherapy. Of the 10 women attempting pregnancy, 6 conceived spontaneously, delivering full-term, unaffected infants. Coincidentally, all pregnancies were in patients who had a cystectomy. There was no relationship between poor outcome, recurrence, implant, or subsequent pregnancy and intraoperative rupture. Although this report suggests that a laparoscopic approach is safe, this is a small series with a short follow up. More data and longer follow up are needed to determine its safety.

Invasive Epithelial Tumors

Contrary to germ cell and low malignant potential tumors, invasive epithelial cell cancers rarely occur in women of reproductive age, with only 7% to 8% of Stage I cancers occurring in women under age 35. A unilateral salpingo-oophorectomy and a full staging procedure is performed in patients desiring fertility preservation with Stage I disease. Meticulous examination of the contralateral ovary is necessary, with biopsies only when grossly visible abnormalities are seen. The potential for a second primary in the contralateral ovary must be
weighed against the age of the patient, the desire to maintain fertility potential, and the likelihood of a successful pregnancy.119

Schilder et al. conservatively treated 52 patients with either Stage IA or IC epithelial ovarian cancer (Grades 1 to 3) with a unilateral salpingo-oophorectomy and staging procedure. The estimated 5-year and 10-year survival rates, using the Kaplan-Meier method, were 98% and 93%, respectively, comparable to reported survival rates of patients treated more aggressively with a total abdominal hysterectomy and bilateral salpingo-oophorectomy. There were five tumor recurrences, two with distant metastases who are dead of disease. Twenty-four patients attempted pregnancies, 17 of whom conceived (71%); 6 of these had received chemotherapy. These 17 women delivered a total of 26 term pregnancies with no congenital anomalies. These authors recommend follow up every 3 months with transvaginal ultrasound and cancer antigen 125 levels for a minimum of 2 years.119

Although most of the published studies have demonstrated the safety of conservative surgery, most authors recommend performing a total abdominal hysterectomy with removal of the remaining ovary after childbearing, without any data to support this recommendation. In our opinion, if many years have elapsed and the patient is without evidence of disease, continued follow up without surgical intervention is rational. However, for breast cancer gene 1/2 mutation carriers, surgery after childbearing is recommended.

Endometrial Cancer

Only 7.9% of endometrial cancers occur in women under 45 years of age, accounting for more than 1,800 new cases annually in the United States.57 Younger women with endometrial cancer tend to have well-differentiated lesions confined to the endometrium, with good outcomes, achieving 5-year survival rates of 95%.120 Atypical endometrial hyperplasia, an endometrial cancer precursor, also occurs less frequently in younger women than in older women. The standard treatment of endometrial cancer is hysterectomy and bilateral adnexectomy, with or without lymphadenectomy depending on the characteristics of the tumor. The treatments for atypical endometrial hyperplasia include hysterectomy with or without adnexectomy versus medical therapies, depending on the patient’s age and desire for future fertility.

Progestins have been routinely used to treat simple hyperplasia and complex hyperplasia without atypia in young women. Typically, progestin (usually medroxyprogesterone acetate [Provera] 10 mg) is administered either for 10 to 14 days each month or continuously for 3 to 6 months, with reported regression in 98% to 100% of patients. The oral contraceptive pill has also been successfully used. Depot medroxyprogesterone acetate ([Depo-Provera] 150 mg intramuscularly every 3 months) can be given to women for whom compliance is an issue. In young women with atypical hyperplasia, an alternative to hysterectomy is treatment with megestrol ([Megace] 40 mg, 2–4 times daily for 3–12 months) with reported regression rates of 94%.121

Successful progestin therapy for the treatment of endometrial cancer is not as well documented. Imai et al. treated 15 young patients (aged 24–38 years) with Grade 1 to 2 endometrial cancer with high dose medroxyprogesterone acetate (400–800 mg) daily for 18 to 64 weeks, with a median treatment length of 29 weeks. Endometrial sampling was performed every 4 weeks. Prescription medroxyprogesterone acetate was maintained for 8 to 12 weeks after regression of the lesion (by sampling). Cyclic medroxyprogesterone acetate therapy (10 mg orally for 14 days per month) was given after the high-dose medroxyprogesterone acetate. The patients were followed for a mean of 59 months from the beginning of progestin therapy. Seven of the 12 patients with Grade 1 carcinoma and 1 of the 2 with Grade 2 carcinoma were documented as having a regression of the cancer (53%). Three of the initial responders and 1 additional patient on maintenance therapy (50%) recurred 19 to 28 weeks after discontinuation of treatment. Seven of 15 (47%) patients had persistent cancer, 1 of whom was found to have deep myometrial invasion with extension to the right ovary.
Eight patients underwent hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomies. One patient with an initial response and then a recurrence was lost to follow up. The other 14 are alive and well. Of the six patients attempting to conceive, two were successful, both requiring assisted reproductive technology. They delivered healthy, full-term infants.\textsuperscript{122}

Randall reported that 16 of 17 women with atypical hyperplasia and 9 of 12 (75\%) women with endometrial cancer were successfully treated with progestins. All treatment failures were persistent lesions, with no progression or metastatic disease. The median length of treatment was 9 months, with a median follow up of 40 months. All women were alive and well and without evidence of disease at the conclusion of the study period. Of the 25 women attempting pregnancy, 5 delivered 7 healthy, full-term infants. Multiple treatment dosages and regimens were used, so no definitive treatment recommendations were made.\textsuperscript{121}

Kim et al. reviewed their experience with progestin therapy for Grade 1 endometrial cancer and combined their series with a review of the literature from 1985 to 1995. In their experience, 4 of 7 patients responded to progestin therapy; however, 50\% of these initial responders had a recurrence 12 to 21 months after completion of treatment. No one delivered a viable infant after treatment in their series. Of note, four of the patients were obese and were thought to have polycystic ovarian syndrome, and two had a history of infertility. The literature review revealed 14 patients treated with progestins, 9 of whom responded to progestin therapy, with only 1 patient having a recurrent tumor. In this patient, at laparotomy, extraterine spread was discovered. She received postoperative radiation and depot-medroxyprogesterone acetate, and 27 months after surgery had regional metastases. She is alive with disease. Seven of 14 patients were obese and were considered to have polycystic ovarian syndrome. When combining Kim’s data and the data from the literature review, 13 of 21 patients (62\%) initially responded to therapy with progestins. Nineteen of 21 patients were alive and without evidence of disease at follow up, and 2 were alive with disease. Three patients developed recurrent disease, of which one was retreated with progestin and alive with disease at the time of publication. Six viable infants were delivered. Of note, the 19 patients alive without evidence of disease include those who had a recurrence and were salvaged with hysterectomy, as well as those who did not respond and underwent hysterectomy for failed medical therapy.\textsuperscript{125}

In another review, Plante reported that there have been a total of about 20 successful pregnancies following the pharmacologic reversal of endometrial carcinoma, with most women free of disease. Most have conceived naturally and fairly rapidly after reversal of their cancer. In some cases, patients safely received clomiphene citrate (Clomid) and IVF. Based on the review, Plante recommended that patients with Grade 2 or higher not be conservatively managed with progestins, as these agents may be less effective in such lesions.\textsuperscript{96} This is a biologically plausible recommendation as progesterone receptors are associated with well-differentiated tumors.

Of note, there has been a 16\% to 29\% rate of ovarian metastasis or synchronous ovarian and endometrial cancer reported in young patients. Treating these patients with progestin therapy alone does not address a potential ovarian cancer, possibly delaying treatment for an undiagnosed malignancy.\textsuperscript{96} Possible etiologies of endometrial cancer are polycystic ovarian syndrome, obesity, or an undiagnosed granulosa cell tumor or other estrogen secreting tumor of the ovary. Thus, it is incumbent that the physician rule out an underlying ovarian tumor before the initiation of progestin treatment.

Based on the small number of patients conservatively treated, the option should be used in very select cases. In a highly motivated patient with a Stage IG1 lesion, the option can be discussed. Consultation with a gynecologic oncologist and a review of the pathology by an outside laboratory should be performed. A hysteroscopy and curettage should be performed to assess the entire endometrial cavity. An ultrasound and cancer antigen 125 test should be
done to assess the ovaries. There may be a role for pelvic magnetic resonance imaging or sonography to evaluate the depth of myometrial invasion. Megace 40 mg 4 times daily for 3 months followed by 20 mg 4 times daily is 1 treatment option. If the patient has any bleeding on this regimen, the endometrial cavity needs immediate reassessment. An endometrial biopsy should be performed at 3 to 6 months. Following treatment, the patient should attempt pregnancy. If patients do not have a contraindication, oral contraceptive pills may be used once the endometrium has been converted to normal.

Testicular Cancer

Testicular tumors are among the most common tumors that affect young men, and 83.7%—more than 4,400 cases—are diagnosed in the United States annually among men younger than 45 years. Patients with testicular cancer have an excellent prognosis, with a relative 5-year survival exceeding 95%, and fertility is one of the main concerns of survivors. The first challenge regarding fertility of testicular cancer survivors is that many have quantitative and qualitative deficiencies in spermatogenesis. These have been frequently observed in men without cryptorchidism or other apparent anatomic explanations.

Virtually all patients will undergo surgical removal of the affected testicle and receive postoperative chemotherapy and/or radiotherapy. The usual regimens are bleomycin, etoposide, and cisplatin or etoposide and cisplatin. Regimens including ifosfamide, vinblastine, cisplatin, and/or paclitaxel may be used to treat recurrent or residual disease. Platinum-based regimens have documented testicular toxicity. Among men who were normospermic before treatment, 16% were oligospermic and 20% azoospermic 1 year after treatment. Spermatogenesis continued to improve over the subsequent 5 years, however.

Radiotherapy (recommended for some men with seminoma) has a much more deleterious effect on fertility, compared with chemotherapy alone. In a recent study of 451 patients, 91.2% who had tried to father a child before treatment were successful, as compared with 67.1% who tried after treatment. Among couples seeking pregnancy, the 5-year cumulative incidence of pregnancy for partners of men treated with surgery and chemotherapy only was approximately 85%; when treatment includes radiotherapy, the incidence was less than 65%. Among men who become azoospermic after radiotherapy (32 Gy), recovery of spermatogenesis occurs 30 to 80 weeks after start of treatment.

Before availability of effective chemotherapy regimens for testicular cancer, full bilateral retroperitoneal lymph node dissections were sometimes used in patients with nonseminomatous germ cell tumors. Damage to nerves of the hypogastric plexus from this procedure almost invariably resulted in retrograde ejaculation, a condition in which erectile function remains intact but where most of the semen from ejaculation is deposited in the bladder rather than exiting the distal urethra. The indications and surgical techniques for retroperitoneal lymph node dissection (RPLND) have evolved substantially during the past several decades, and some form of this procedure is still used, especially for low stage nonseminomatous germ cell tumors. Modified bilateral template RPLND, as used during the early 1980s, preserved antegrade ejaculation in 11% of survivors, and nerve-sparing RPLND preserved antegrade ejaculation in 89%. The current techniques for template dissections allow preservation of the contralateral (to the testicular tumor) nerves, and antegrade ejaculation is intact in approximately 80%. Even when retrograde ejaculation occurs, spermatozoa for assisted reproduction methods can be obtained from urine shortly after ejaculation.

CONCLUSIONS

As the demand for fertility-sparing options grows among young women and men with cancer, the medical community has responded to these demands with more conservative surgical and medical therapies. Patients need to be made aware of their options. Reproductive endocrinologists and
urologists continue their efforts to perfect cryopreserving technologies to retain ovarian and testicular function. Conservative treatment is an option in highly motivated young women desiring future fertility with certain cancers of the reproductive tract. Informed decision making is essential. Patients must be aware of the standard therapies, risks and benefits of conservative treatment, and need for careful follow up.

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cancer. Influence to fertility. Strahlenther Onkol 2003;179:754–759.

40. Shalet SM, Tsatsoulis A, Whitehead E, Read G. Vulnerability of the human Leydig cell to radiation damage is dependent upon age. J Endocrinol 1989;120:161–165.

41. Gordon W Jr, Siegmund K, Stanisic TH. A study of reproductive function in patients with seminoma treated with radiotherapy and orchidectomy: (SWOG-8711). Southwest Oncology Group. Int J Radiat Oncol Biol Phys 1997;38:83–94.

42. Thomson AB, Campbell AJ, Irvine DC, et al. Semen quality and spermatozoal DNA integrity in survivors of childhood cancer: a case-control study. Lancet 2002;360:361–367.

43. Chatterjee R, Haines GA, Perera DM, et al. Testicular and sperm DNA damage after treatment with fludarabine for chronic lymphocytic leukemia. Hum Reprod 2000;15:762–766.

44. Schmiegelow ML, Sommer P, Carlsen E, et al. Penile vibratory stimulation and electroejaculation before anticancer therapy in two pubertal boys. J Pediat Hematol Oncol 1998;20:429–430.

45. Park YS, Lee SH, Song SJ, et al. Influence of motility on the outcome of in vitro fertilization/ intracytoplasmic sperm injection with fresh vs. frozen testicular sperm from men with obstructive azoospermia. Fertil Steril 2003;80:526–530.

46. Kliesch S, Behre HM, Jurgens H, et al. Cryopreservation of semen from adolescent patients with malignancies. Med Pediatr Oncol 1996;26:20–27.

47. Schover LR, Brey K, Lichtin A, et al. Oncologists’ attitudes and practices regarding banking sperm before cancer treatment. J Clin Oncol 2002;20:1890–1897.

48. Schover LR, Brey K, Lichtin A, et al. Knowledge and experience regarding cancer, infertility, and sperm banking in younger male survivors. J Clin Oncol 2002;20:1880–1889.

49. Sanger WG, Olson JH, Sherman JK. Sperm cryopreservation for use with cancer-criteria change. Fertil Steril 1992;58:1024–1027.

50. Radford J, Shalet S, Lieberman B. Fertility after treatment. Questions remain over of preserving ovarian and testicular tissue. BMJ 1999;319:935–936.

51. Audrins P, Holden CA, McLachlan RI, et al. Semen storage for special purposes at Monash IVF. BMJ 1999;319:935–936.

52. Meistrich ML, Byrne J. Genetic disease in offspring of long-term survivors of childhood and adolescent cancer treated with potentially mutagenic therapies. Am J Hum Genet 2002;70:1069–1071.

53. Partridge AH, Garber JE. Long-term outcomes of children exposed to antineoplastic agents in utero. Semin Oncol 2000;27:712–726.

54. Ries LAG, Eisner MP, Kosary CL, et al. (eds). SEER Cancer Statistics Review, 1975–2001. Bethesda, MD: National Cancer Institute. Available at: http://seer.cancer.gov/csr/1975_2001/. Accessed 2004.

55. Partridge AL, Gelber S, Knudsen K, et al. Web-based survey of fertility issues in young women with breast cancer. J Clin Oncol 2004;22:4174–4183.

56. Burstyn HJ, Winer EP. Reproductive issues, in Harris JR (ed). Diseases of the Breast. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2000;1051–1059.

57. Minton SE, Munster PN. Chemotherapy-induced amenorrhea and fertility in women undergoing adjuvant treatment for breast cancer. Cancer Control 2002;9:466–472.

58. Burstyn HJ, Winer EP. Primary care for survivors of breast cancer. N Engl J Med 2000;343:1086–1094.

59. Hortobagyi GN, Buzdar AU, Marcus CE, Smith TL. Immediate and long-term toxicity of adjuvant chemotherapy regimens containing doxorubicin in trials at M.D. Anderson Hospital and Tumor Institute. NCI Monogr 1986;1:101–109.

60. Valagusa P, De Candis D, Antonelli G, Bonadonna G VIII. Women’s health perception and breast cancer: issues of fertility, hormone substitution, and cancer prevention. Recent Results Cancer Res 1996;140:277–283.

61. Weber B, Luporsi E. Ovarian toxicity of breast cancer chemotherapy. Eur J Cancer 1998;34(Suppl 3):S42.

62. Goodwin PJ, Ennis M, Pritchard KL, et al. Risk of menopausal changes during the first year after breast cancer diagnosis. J Clin Oncol 1999;17:2365–2370.

63. Partridge AH, Burstyn HJ, Winer EP. Side effects of chemotherapy and combined chemo-hormonal therapy in women with early-stage breast cancer. J Natl Cancer Inst Monogr 2001;(30):135–142.

64. Stone ER, Slack RS, Novielli A, et al. Rate of chemotherapy related amenorrhea (CRA) associated with adjuvant adriamycin and cytoxan (AC) and adriamycin and cytoxan followed by taxol (AC+T) in early stage breast cancer [abstract 224]. Breast Cancer Res Treat 2000;64:66.

65. Fox KR, Scialla J, Moore H. Preventing chemotherapy-related amenorrhea using leuprolide during adjuvant chemotherapy for early-stage breast cancer [abstract S50]. Proc Am Soc Clin Oncol 2003;22:13.

66. Partridge A, Gelber S, Peppercorn J, et al. Fertility outcomes in young women with breast cancer: a Web-based survey [abstract 6085]. Proc Am Soc Clin Oncol 2004;23:S38.

67. Danforth DN Jr. How subsequent pregnancy affects outcome in women with a prior breast cancer. Oncology (Huntingt) 1991;5:23–30; discussion 30–21, 35.

68. Kroman N, Jensen MB, Melbye M, et al. Should women be advised against pregnancy after breast cancer treatment? Lancet 1997;350:319–322.

69. Sankila R, Heimavara S, Hakulinen T. Survival of breast cancer patients after subsequent term pregnancy: “healthy mother effect”. Am J Obstet Gynecol 1994;170:818–823.

70. von Schoultz E, Johanson H, Wilkink N, Rutsigv E. Influence of prior and subsequent pregnancy on breast cancer prognosis. J Clin Oncol 1995;13:430–434.

71. Petrok JA. Pregnancy safety after breast cancer. Cancer 1994;74(1 Suppl):528–531.

72. Sembone A, Petrok JA. Childbearing issues in breast cancer survivors. Cancer 1997;79:1271–1278.

73. Gemignani ML, Petrok JA. Pregnancy after breast cancer. Cancer Control 1999;6:272–276.

74. Velentgas P, Daling JR, Malone KE, et al. Pregnancy after breast carcinoma: outcomes and influence on mortality. Cancer 1999;85:2424–2432.

75. Dow KH, Harris JR, Roy C. Pregnancy after breast-conserving surgery and radiation therapy for breast cancer. J Natl Cancer Inst Monogr 1994;16:131–137.

76. Higgin S, Haffty BG. Pregnancy and lactation after breast-conserving therapy for early stage breast cancer. Cancer 1994;73:2175–2180.

77. Gelber S, Coates AS, Goldhirsh A, et al. Effect of pregnancy on overall survival after the diagnosis of early-stage breast cancer. J Clin Oncol 2001;19:1671–1675.

78. Upponi SS, Ahmad F, Whitaker IS, Purnashotham AD. Pregnancy after breast cancer. Eur J Cancer 2003;39:736–741.

79. Mueller BA, Simon MS, Deapen D, et al. Childbearing and survival after breast carcinoma in young women. Cancer 2003;98:1131–1140.

80. Blakely L, Buzdar AU, Lozada JA, et al. Effects of pregnancy after treatment for breast carcinoma on survival and risk of recurrence. Cancer 2004;100:465–469.

81. Nygaard AR, Clausen S, Siimes MA, et al. Reproduction following treatment for childhood leukemia: a population-based prospective cohort study of fertility and offspring. Med Pediatr Oncol 1991;19:459–466.

82. Byrne J, Fears TR, Mills JL, et al. Fertility in women treated with cranial radiotherapy for childhood acute lymphoblastic leukemia. Pediatr Blood Cancer 2004;42:589–597.

83. Byrne J, Fears TR, Mills JL, et al. Fertility of long-term survivors of acute lymphoblastic leukemia diagnosed during childhood. Pediatr Blood Cancer 2004;42:364–372.

84. Klein CE. Gonadal Complications, in Kufe DW, Pollock R, Weichselbaum RR, et al. (eds). Cancer Medicine. 6th ed. Hamilton, Ontario: BC Decker, Inc.;2003:2189–2210.

85. Meistrich ML, Vassilopoulos-Sellin R, Lipshultz LI. Gonadal Dysfunction, in DeVita VT,
103. Schorge JO, Lee KR, Sheets EE. Prospective management of stage IA(1) cervical adenocarcinoma by conization alone to preserve fertility: a preliminary report. Gynecol Oncol 2000;78:217–220.

104. Schlaerth JB, Sports NM, Schlaerth AC. Radical trachelectomy and pelvic lymphadenectomy with uterine preservation in the treatment of cervical cancer. Am J Obstet Gynecol 2003;188:29–34.

105. Coven A, Shaw P, Murphy J, et al. Is radical trachelectomy a safe alternative to radical hysterectomy for patients with Stage IA–IB carcinoma of the cervix? Cancer 1999;86:2273–2279.

106. Dargent D, Martin X, Sacchetoni A, Mathevet P. Laparoscopic vaginal radical trachelectomy. Cancer 2000;88:1877–1882.

107. Roy M, Plante M. Pregnancies after radical vaginal trachelectomy for early-stage cervical cancer. Am J Obstet Gynecol 1998;179:1491–1496.

108. Rodriguez M, Guimaraes O, Rose P. Radical abdominal trachelectomy and pelvic lymphadenectomy with uterine conservation and subsequent pregnancy in the treatment of early invasive cervical cancer. Am J Obstet Gynecol 2001;185:370–374.

109. Windischler GH, Muller-Holzner E, Nicolussi-Leck G, et al. Ovarian preservation in the surgical treatment of cervical carcinoma. Am J Obstet Gynecol 1999;180:963–969.

110. Aubard Y, Piver P, Pech JC, et al. Ovarian tissue cryopreservation and gynecologic oncology: a review. Eur J Obstet Gynecol Reprod Biol 2000;97:5–14.

111. Buekers TE, Anderson B, Sorosky JL, Buller RE. Ovarian function after surgical treatment for cervical cancer. Gynecol Oncol 2001;80:85–88.

112. Fujiwara K, Mohri H, Yoshida T, et al. Subcutaneous transposition of the ovary following hysterectomy. Int J Obstet Gynecol 1997;58:223–228.

113. Mishell DR, Stenchever MA, Droegemueller W, Herbst AL. Comprehensive Gynecology. St. Louis, MO: Mosby; 1997.

114. Brewer M, Gershenson DM, Herzog CE, et al. Outcome and reproductive function after chemotherapy for ovarian dysgerminoma. J Clin Oncol 1999;17:2670–2675.

115. Gershenson DM. Menstrual and reproductive function after treatment with combination chemotherapy for malignant ovarian germ cell tumors. J Clin Oncol 1988;6:270–275.

116. Kanazawa K, Suzuki T, Sakamoto K. Treatment of malignant ovarian germ cell tumors with preservation of fertility: reproductive performance after persistent remission. Am J Clin Oncol 2000;23:244–248.

117. Serachioti R, Venturoli S, Colombo FM, et al. Fertility and tumor recurrence rate after conservative laparoscopic management of young women with early-stage borderline ovarian tumors. Fertil Steril 2001;76:999–1003.

118. Morice P, Carmatte S, Hassan JE, et al. Clinical outcomes and fertility after conservative treatment of ovarian borderline tumors. Fertil Steril 2001;75:92–96.

119. Schilder T, Thompson A. Outcome of reproductive age women with Stage IA or IC invasive epithelial ovarian cancer treated with fertility-sparing therapy. Gynecol Oncol 2002;87:1–7.

120. Wang CB, Wang CJ, Huang HJ, et al. Fertility-preserving treatment in young patients with endometrial adenocarcinoma. Cancer 2002;94:2192–2198.

121. Randall TC, Kurman RJ. Progestin treatment of atypical hyperplasia and well-differentiated carcinoma of the endometrium in women under age 40. Obstet Gynecol 1997;90:434–440.

122. Imai M, Jobo T, Sato R, et al. Medroxyprogesterone acetate therapy for patients with adenocarcinoma of the endometrium who wish to preserve the uterus-usefulness and limitations. Eur J Gynaecol Oncol 2001;22:217–220.

123. Hendry WF, Stedronska J, Jones, CR, et al. Semen analysis in testicular cancer and Hodgkin’s disease. Pre- and post-treatment findings and implications for cryopreservation. Br J Urol 1983;5:769–773.

124. Lampe H, Horwich A, Norman A, et al. Fertility after chemotherapy for testicular germ cell cancers. J Clin Oncol 1997;15:239–245.

125. Kim YB, Holchneider CH, Ghosh K, et al. Progestin alone as primary treatment of endometrial carcinoma in premenopausal women. Cancer 1997;99:320–327.

126. Huyge E, Matsuda T, Daudin M, et al. Fertility after testicular cancer treatments: results of a large multicenter study. Cancer 2004;100:732–737.

127. Hahn EW, Feingold SM, Simpson L, Batata M. Recovery from aspermia induced by low-dose radiation in seminoma patients. Cancer 1983;50:337–340.

128. Jacobsen KD, Ous S, Warøe H, et al. Ejaculation in testicular cancer patients after post-chemotherapy retroperitoneal lymph node dissection. Br J Cancer 1999;80:249–255.

129. Sheinfeld J, Herr H. Role of surgery in management of germ-cell tumors. Semin Oncol 1998;25:203–209.