Fertility preservation for nonmalignant medical conditions

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Over the past decade, researchers, clinicians and patients have advocated the importance of preserving fertility in young people facing potentially sterilizing treatments for diseases such as cancer. In 2005, the American Society of Clinical Oncology (ASCO), American Society for Reproductive Medicine, Association of Pediatric Hematology/Oncology Nurses and other organizations began publishing a series of fertility preservation guidelines for cancer patients. The guidelines urge clinicians to counsel patients as early as possible about cancer therapy’s effects on fertility and the strategies for mitigating such effects.1-3 In 2007, the Oncofertility Consortium was established to develop new fertility preservation technologies for young cancer patients and ensure that fertility preservation options are incorporated into clinical oncology management plans.

With time, it has become clear that fertility preservation is a concern for an even broader patient population, including those with nonmalignant diseases and others facing treatments with potentially iatrogenic effects on fertility.4 For example, rheumatologic disorders, nonmalignant hematologic conditions, neurologic disorders, renal disorders and other similar conditions can disrupt the reproductive axis. However, providers and patients have little information about these effects on fertility, as the negative consequences of various disease treatments and procedures are only now being appreciated. These nonmalignant diseases and their treatments can reduce gonadal, endocrine or sexual function for men and women and affect a woman’s ability to carry a pregnancy to term. But given the success of fertility preservation strategies first developed for young cancer patients, clinical practitioners now have the ability to implement fertility preservation options for a broader group of patients.

Reproductive consequences of medical interventions

Disease treatment can cause hormonal impairments or structural damage to reproductive organs. However, most studies investigating iatrogenic effects on fertility rely on indirect measures of fertility, making it difficult to assess the exact effects treatment might have on later reproductive ability. In women, these measures include resumption of menstrual cycles, antral follicle count and hormone levels, such as anti-mullerian hormone or follicle-stimulating hormone. In males, fertility assessment most often includes a semen analysis to identify sperm count, mobility and motility.

Women who conceive after disease treatment should understand how previous chemotherapy and pelvic radiation might affect their ability to carry a pregnancy to term. Studies consistently report that past chemotherapy and radiation treatment do not result in increased rates of birth defects for offspring of disease survivors. However, the risk for preterm delivery, low infant birth weight and cesarean section is greater for cancer survivors and those who have undergone stem cell transplantation.5,6 As a result, the only direct assessment of reproductive function is the conception and live birth of a child.

In females, chemotherapy and radiation can also cause loss of endocrine hormones, such as estrogen. Reduced estrogen can result in premature menopausal symptoms, including diminished bone health, cognitive disruption, profound
changes in body temperature, sleep difficulties, vaginal dryness and cardiovascular changes.\textsuperscript{7,8} In males, chemotherapy and radiation may result in increased follicle-stimulating hormone and reduced testosterone.\textsuperscript{9} Pediatric patients may experience additional effects of treatment, such as precocious or delayed puberty and related physical and psychological disruptions.\textsuperscript{10}

Fertility preservation is available for most patients facing a potentially sterilizing disease treatment. While reproductive function has been investigated to varying degrees in patients with nonmalignant diseases and treatments, a patient’s decision regarding whether or not to undergo fertility preservation relies on that patient’s knowledge of the relative reproductive risks of treatment and the existing options for preserving fertility prior to treatment. We address these considerations in the context of hematologic diseases, autoimmune disorders and surgical interventions.

\textbf{Hematologic diseases}
Nonmalignant hematologic conditions, such as thalassemia major, sickle cell anemia, aplastic anemia, Fanconi anemia and myeloproliferative diseases, can be treated with bone marrow transplantation or hematopoietic stem cell transplantation, which can impair future fertility. Over the past 20 years, stem cell transplantation rates have increased significantly due to increasing success. However, preconditioning high-dose chemotherapy with alkylating agents and whole-body radiation can have striking effects on later reproductive ability. As few as 6 percent of women undergoing preconditioning whole-body radiation may have spontaneous resumption of the menstrual cycle.\textsuperscript{11,12} Patient age has a significant effect on this outcome. In one study, 12 percent of women age 24 and younger resumed menses while none of the women age 25 and older did. As with cancer treatment, other significant risk factors for infertility after preconditioning are the total amount of radiation and the type and amount of chemotherapy.\textsuperscript{5,11} Pediatric patients may be at differential risk for infertility, as a recent study identified that prepubertal males are at greater risk for reproductive disruption after stem cell transplantation than those undergoing transplantation after puberty. In contrast, females age 13 or older are more likely than younger girls to experience fertility damage.\textsuperscript{13}

Iatrogenic infertility may also result from blood transfusion therapy for thalassemia major, chronic hemolytic anemia, sickle cell anemia and other conditions that can cause excessive iron accumulation in the body. In women, this hemochromatosis causes iron deposition in the anterior pituitary, leading to subsequent hormonal and reproductive dysfunction. In men, iron buildup can occur in the testes, resulting in reproductive dysfunction. Given the significant possible reproductive effects of treatments for nonmalignant hematologic conditions, healthcare providers should counsel patients about each treatment’s effects on future fertility and strategies for mitigating those effects.

\textbf{Autoimmune disorders}
Severe autoimmune diseases, including systemic lupus erythematosus (SLE), multiple sclerosis (MS), chronic kidney diseases and rheumatoid arthritis, may also require interventions that disrupt reproductive function. Many of these autoimmune disorders develop during reproductive years, predominantly among women. More than 90 percent of the 1.5 million to 2 million people with SLE are women in their childbearing years.\textsuperscript{4} Females with SLE may be at increased risk for pregnancy loss as well as severe kidney disease, which has its own reproductive consequences. Males with SLE may experience erectile dysfunction or decreased spermatogenesis.

Severe cases of autoimmune diseases now call for the use of fertility-impairing chemotherapeutic treatments, including alkylating drugs. Lupus nephritis or other severe forms of lupus may require treatment with drugs such as cyclophosphamide. Juvenile SLE is also regularly treated with drugs that may impair fertility. Furthermore, adolescent treatment with alkylating agents, steroids or antiphospholipid antibodies, in addition to autoimmune oophoritis in adolescents with juvenile SLE, may result in primary ovarian insufficiency. Amenorrhea after alkylating agent treatment for autoimmune diseases can vary based on the frequency and length of exposure, age of patient and concurrent treatments. Between 27 percent
and 60 percent of women with SLE who are treated with cyclophosphamide report amenorrhea, with the majority of these patients experiencing amenorrhea for more than a year.4

Like SLE, MS affects women more than twice as often as men, typically during reproductive years. Most patients with MS do not require fertility-impairing therapies. However, patients with severe forms of MS, such as progressive MS or treatment-resistant MS, may require alkylating chemotherapeutics, such as mitoxantrone, which has gonadotoxic effects. Mitoxantrone treatment can result in amenorrhea rates of around 30 percent after treatment, and these risks increase with patient age.4 Nonsteroidal anti-inflammatory drugs (NSAIDs) are a common treatment for autoimmune disorders. NSAIDs suppress inflammation and have a variety of additional downstream effects, including the inhibition of prostaglandins, which are integral to ovulation. Thus, NSAID treatment may result in reversible yet reduced fertility in women with autoimmune disorders.

As with hematologic conditions, severe cases of autoimmune disorders are increasingly treated with stem cell transplantation, which requires the considerations discussed earlier. In addition to iatrogenic effects, the diseases themselves can cause symptoms that reduce female sexual function and fertility and disrupt the ability to carry a pregnancy to term. Advances in medical treatments have resulted in better prognoses and long-term quality of life for many patients living with autoimmune conditions. This makes it even more important that the healthcare community include reproductive health in clinical discussions with these patients.

Surgical interventions
Surgical treatments for a variety of diseases may disrupt fertility, and patients should receive appropriate counseling regarding options for preserving reproductive ability prior to medical intervention.

Pelvic surgery may affect later fertility for patients with nonmalignant conditions. Inflammatory bowel disease, ulcerative colitis, familial adenomatous polyposis and other diseases may require surgery that can shift pelvic organs and cause postsurgical scarring and adhesions, which may result in reduced fertility.4

Patients who undergo organ transplantation may also face reproductive consequences. Reproductive function is usually normal in kidney, liver and other transplant patients. However, reproductive counseling for these patients is important, as the timing of pregnancy after transplant and related immunosuppressive medicines may affect fetal development and pregnancy outcomes.15,16

Condition-associated infertility
Fertility preservation may also be appropriate when a medical condition, rather than its treatment, can reduce fertility. Obesity and related conditions, such as polycystic ovarian syndrome and diabetes, are examples of fertility-impairing diseases of significant concern.17 Other conditions, such as celiac disease and the autoimmune diseases discussed earlier, may also cause infertility or reduced fertility. However, further study is needed to determine the absolute risks in these patient populations.18 Furthermore, patients with genetic conditions that can cause reduced fertility or early-onset menopause may benefit from fertility preservation. As such, healthcare providers should understand the effects these disorders have on reproductive ability.

X-linked disorders
Certain genetic conditions may cause reduced fertility or premature infertility in both sexes. In women, these conditions may include Turner syndrome, Fragile X premutations and X chromosome deletions. In males, Klinefelter syndrome was previously associated with absolute sterility, but now provides an opportunity for fertility preservation. In some cases, patients with these genetic backgrounds could benefit from early discussions of fertility preservation.

Turner syndrome has a highly variable expression and a range of reproductive consequences. The variability of this X-linked disorder is principally dependent on the mosaic expression of the X chromosome. However, the majority of women with Turner syndrome experience premature degeneration of the ovarian follicles, which leads to premature ovarian failure. Recent clinical reports indicate that embryo or oocyte cryopreservation may be an option for these women, as younger adult patients respond to hormonal stimulation prior to oocyte retrieval. For
adolescent females, ovarian tissue cryopreservation may be an option, though the best use of such tissue is not yet standardized. Women with Turner syndrome often have additional manifestations of the syndrome, such as cardiac anomalies, which are contraindicated for pregnancy. Thus, healthcare providers should incorporate the subject of gestational carriers into fertility preservation discussions with these women.

Males with Klinefelter syndrome, distinguished by the presence of more than one X chromosome, may have limited spermatozoa, though reports conflict regarding the rate of decline in sperm production over time. As such, it has been suggested that these patients may consider sperm cryopreservation to preserve fertility. Some patients with genetic conditions may wish to have children but have concerns about passing on their genetic background. In these cases, reproductive counseling may include discussions about preimplantation genetic diagnosis of embryos.

Fertility preservation considerations

Young people living with fertility-impairing disease and those facing potentially iatrogenic effects of treatment can consider fertility preservation in a different manner than cancer patients might. Cancer patients must often make fertility preservation decisions immediately after diagnosis and in the relatively short time before beginning treatments with potentially iatrogenic effects. In contrast, young people with rheumatologic disorders, nonmalignant hematologic conditions and other conditions discussed earlier often have significant time to make fertility preservation decisions, identify financial resources and assess their potential reproductive future with a lifelong disease. Furthermore, such patients may consider stem cell transplantation or other treatments with the risk of iatrogenic fertility loss only as a last resort. Thus, individuals with nonmalignant conditions who are facing the possibility of reduced or absent fertility often have a significant amount of time to make decisions regarding fertility preservation.

Communication needs

Healthcare providers should be a gateway for information about reproductive health and fertility preservation, particularly for young patients. Providers can educate young patients about potential iatrogenic effects of treatment, discuss fertility preservation options and provide referrals to local reproductive specialists. Unfortunately, studies have found that less than half of young cancer patients generally receive information about potential fertility loss. Even with increasing advocacy, communication and education from professional groups such as Fertile Hope and ASCO, a 2009 study found that only 61 percent of surveyed cancer patients remembered hearing about the reproductive effects of treatment from their oncology team, and only 4 percent of surveyed patients ultimately chose to undergo fertility preservation.

Research suggests that provider biases might be preventing better provider-patient communication. Oncology providers may be less likely to discuss fertility with patients of lower perceived financial means, but more likely to broach the issue with patients of perceived similar social status. Additional factors can affect provider discussions regarding future reproduction and fertility preservation options, including patient prognosis, age, time before treatment, marital status, sexual orientation and provider assumptions about a patient’s desires to have children. Furthermore, clinicians may underestimate the value a patient places on future reproductive potential if they fail to discuss fertility preservation during an office visit. As such, providers should be aware of these factors to ensure equal treatment of all young patients.

Financial considerations

One of the most common reasons patients ultimately decide not to preserve fertility is cost. Costs for fertility preservation can range from $700 to $900 for sperm cryopreservation and $7,000 to $15,000 for oocyte or embryo cryopreservation, with additional fees for storage and later use of the gametes or embryos. Insurance coverage for fertility preservation in the United States varies widely, depending on the insurance company, state regulations and other factors. Fifteen states currently have fertility mandates that require insurance companies to cover established treatments for patients diagnosed with infertility. However, the insurance industry’s current definition of infertility requires an individual to try to conceive for one year without success. As such, fertility preservation patients do not fall under this mandate, as they
are not infertile at the time of treatment. Through its work with patients, providers and insurance companies, the National Physicians Cooperative of the Oncofertility Consortium has identified a series of mechanisms to call for insurance coverage of fertility preservation, including coding treatment under the primary diagnosis of disease, not infertility, as well as providing letters of appeal to insurance companies.26

Multiple organizations, including Livestrong Sharing Hope, Fertile Action and others, now provide financial support for young cancer patients looking to preserve their fertility. While these programs are designed for cancer patients, they may also offer support for others facing fertility-impairing treatments. An increasing number of programs cover the costs of ovarian stimulation for women prior to oocyte or embryo banking and reduce storage costs for young cancer patients. Though many of these programs are currently restricted to cancer patients, increasing awareness of fertility preservation in nonmalignant conditions may expand their reach.

Conclusion
Over the last decade, research efforts have focused on ensuring cancer survivors a high quality of life, including a reproductive future. Researchers and clinicians can apply these efforts to an even broader scope of conditions and related treatments that might also result in impaired fertility. Patients with these conditions may also benefit from education and guidance regarding appropriate fertility preservation options. As such, providers should be aware of the unique needs of this group, particularly how they compare with the needs of cancer patients.

Reproductive healthcare providers should familiarize themselves with this emerging population of patients and prepare their practices accordingly. In addition, the community of reproductive researchers and healthcare providers should work to educate disease specialists—oncologists, rheumatologists, genetic counselors and others—about the reproductive effects of nonmalignant diseases and their treatments as well as the options for preserving fertility.
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References


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