Fertility perspectives for the cancer patient

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As cancer survival rates continue to improve, as evidenced over the last 20 years, focus begins to shift toward improving quality of life. An aspect of patient care once judged trivial when measured alongside a goal as primary as survival, quality of life has ascended the ladder of care, enabled largely by ongoing advances in reproductive technologies. Several successful fertility preservation and post-treatment parenthood options have emerged to fill the void, prompting cancer patients to seek out previously unavailable information about risks and options. As physicians labor to accommodate burgeoning interest, it is essential that such information be communicated objectively and compassionately to the patient, with thoughtful consideration of his or her cancer type, treatment location, dosage, gender and age.

Reproductive endocrinology and fertility is a singular, distinct discipline focused on treating disorders of the endocrine system wherein the body becomes unable to conceive offspring. For the person with cancer, this focus integrates changes to the reproductive system stemming from cancer therapy. Statistical increases in the number of affected patients diagnosed in their reproductive years and the rate of infertility associated with common cancer therapies have resulted in a sizeable push toward proactive fertility preservation and family planning measures for both men and women. With patient population size on the rise, physicians must address emerging barriers to accessing fertility care, including cost of treatment, insurance restrictions, at-risk potential, scope of treatment options, patient fears and misconceptions about the safety of fertility treatment, and a general deficiency of information provided during and after cancer diagnosis. Current options for treatment-induced infertility offer promise not found with cancer therapies such as chemotherapy, radiation or surgery. And because the risk of infertility extends to nearly all cancer types, ethnicities and both genders, education plays a vital role in the physician-patient relationship. Patient awareness of several key points may facilitate progress in the fertility preservation decision-making process:

- More than 130,000 cancer patients are diagnosed prior to age 45.
- Nearly 25 percent of breast cancer patients are diagnosed prior to age 45.
- 12,000 children ages 0–19 are diagnosed with cancer annually.
- Up to 90 percent of young cancer patients are at risk for infertility.
- Less than 25 percent of oncologists inform eligible patients of their infertility risks and options.
- Cancer treatment may result in premature ovarian failure and increased risk of miscarriage in women and azoospermia in men.
- Probability of treatment-induced menopause increases dramatically with age.
- There are no data to suggest that pregnancy after treatment triggers recurrence.
- Viable options exist for both men and women.

As in non-cancer patients, the mindset of the cancer patient is specific to the individual and should be evaluated during an initial appointment. However, the vulnerability of the patient who has recently been impacted by the presentation of a life-altering disease introduces a unique dynamic into the fold. Fertility preservation affords hope, generating promise for life and legacy, and as such, it has an important role to play in encouraging patients to persevere in their fight against cancer. Fertility options exist for both men and women, including pre-treatment, during treatment, and post-treatment alternatives.

The physiology of fertility

In males, spermatogenesis begins at puberty and continues throughout life. Spermatogenesis is the three-step process by which stem cells develop into mature spermatozoa. In healthy males, the typical sperm cycle lasts 74 days. With age comes a decline in production of spermatozoa. This in itself can be an obstacle to conception. When coupled with cancer therapy, the chances of conception are severely diminished. Females, on the other hand, are born with a volume of eggs to last a lifetime. Just 16–20 weeks after conception, 6–7 million eggs have already been produced. By birth the number has dropped to 2 million, and at puberty only 400,000 exist. This "numbers game" contributes to the body's ability or inability to conceive.

For most healthy couples, conception occurs within six months to a year. But for roughly 15 percent, infertility keeps them from conceiving inside of 12 months. One-third of the

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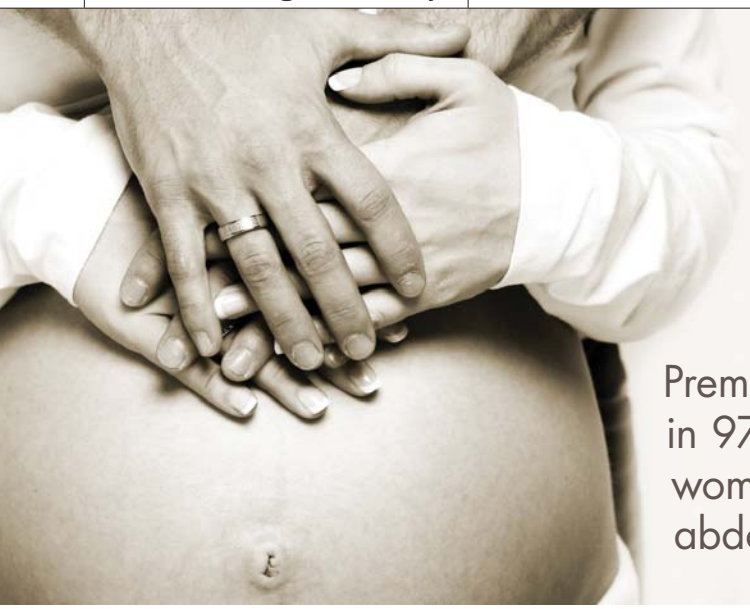

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causes is attributed to female physiological problems, one-third to males and one-third to a combination of factors in couples. These are the basics of infertility. In cancer patients, fertility potential is based not just on gender and normal physiology, but also on type and dosage of therapy.

Effects of cancer therapy

Chemotherapy

Chemotherapy is a systemic treatment that involves the use of chemical agents to stop cancer cells from growing or multiplying. For the more than half of all diagnosed cancer patients treated with chemotherapy, the drug is primarily administered parenterally or orally. Widely considered the best treatment for successful recovery, chemotherapy is designed to kill cancer cells. Unfortunately, the treatment can also kill healthy cells that may affect the patient's ability to conceive. The age of the patient, the course and dose of drug administration, the type of agent used, and gender all play a significant role. There is a high risk of premature ovarian failure, or POF, in women diagnosed at age 30 and older, as well as increased risk of POF in patients age 25 and older at the onset of chemotherapy.

By and large, alkylating agents are the worst offenders for infertility, in that they cause a breakdown of DNA within the body. This prevents normal, mature cells from regenerating. Typically, males are more susceptible and frequently develop oligospermia, or low sperm count, and more frequently azoospermia, or no measurable level of sperm. This is because the testicles sit outside of the body and are more susceptible to external factors. In women, the effects are predominantly on maturing oocytes, with lesser effects on primordial follicles. Transient amenorrhea may transition to POF.

Radiation

Infertility as a result of radiation is highly dependent on dosage. It is also localized. Direct testicular irradiation presents the greatest risk of low sperm levels. POF develops in 97 percent of post-pubertal women treated with total abdominal therapy, and uterine function may be compromised due to impaired blood flow to vital organs.

Fertility preservation options prior to therapy

Options for males

Prior to beginning therapy, post-pubescent males can choose sperm banking, which presents a high rate of success. During an outpatient procedure the sperm cells are donated, analyzed, frozen and stored for a later date. Lower sperm count is no longer an obstacle, thanks to advanced technology like intracytoplasmic sperm injection techniques; however, it is unknown how much damage results if the procedure is done after cancer therapy has been initiated. Sperm levels are affected by frequency of ejaculation, and this should be addressed with the patient for optimal results.

Testicular tissue freezing, another outpatient procedure, is available to both pre- and post-pubescent males. It involves the surgical removal, freezing and storage of testicular tissue, to be thawed at a later date. This procedure can be performed on patients in whom no sperm have been identified. After testicular sperm extraction, the testicular tissue is fragmented and examined, then the sperm removed for freezing or immediate use. Success rates for this procedure range from 30 to 70 percent. Percutaneous epididymal sperm aspiration/microscopic epididymal sperm aspiration and testicular sperm extraction are procedures performed under general anesthesia or local anesthesia with sedation, whereby sperm and testicular tissue are removed from the epididymis and testes, respectively, by use of a fine-gauge needle. Both procedures are generally used in conjunction with intracytoplasmic sperm injection to directly inject a single sperm into a mature egg.

In those cases where viable sperm are unavailable, donor sperm can be used for conception. Males can choose sperm from a donor who has similar genetic makeup, educational record or talents, to be used with eggs from their female partner. In some instances, a male patient may select sperm to be donated from a male family member, such as a brother or cousin, but it is important to note that this would be subject to the guidelines set up by the American Society of Reproductive Medicine.

Options for females

Drug therapy can be administered during chemotherapy treatment, inducing a hypogonadotropic hypogonadal state of temporary "medical menopause" that reduces damage to immature follicles, and consequently reduces risk of infertility. The most common drug therapy is gonadotropin-releasing hormone agonists. This therapy may be employed in post-pubescent females; however, certain side effects may present. These include, but are not limited to, hot flushes, headaches, mood swings, vaginal dryness and, in some cases, osteopenia. While animal data show that Rhesus monkeys treated with agonist prior to chemotherapy lost only 24 percent of primordial follicles, compared to controls that lost 64 percent, most studies produce human data suggesting no effect.

In-vitro fertilization is another option, affording women the chance to obtain and freeze eggs. Standard protocols take 2–6 weeks, so the time necessary to complete the procedure may play a negative role with respect to certain therapies. It is unclear whether increased estrogen levels adversely affect breast cancer risks.

The first use of frozen oocytes or embryos resulting in a live human birth was more than 20 years ago. Success rates now are dramatic. Physician challenges may include preserving the egg's ability to fertilize as well as preserving the integrity of the genetic material within the oocyte. Due to crystallizing of organelles, risk lies not with the freezing, but with the thawing. However, this can be a viable option for pre- and post-pubertal oocytes.

Another fertility preservation alternative is ovarian tissue freezing, which can be done laparoscopically. The ovarian cortex is removed, cut into strips and cryopreserved for later reimplantation. Stimulation is required for mature oocytes, which might require a delay in cancer treatment. Ovarian tissue removal requires surgery, and there exists a risk of reemerging cancer or activation of dormant cancer cells.

Donor oocytes and donor embryos represent the best of assisted reproductive technology and highest success rate, at 75–80 percent per cycle. This high rate of success is attributed primarily to the use of young, healthy oocytes and the opportunity to prime the uterine lining for receptive implantation.

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Finally, surrogacy offers a controllable uterine lining and utilizes fresh embryos for transfer, resulting in high success rates. The uncontrollable factor is the age of the egg, which is the age of the donor. Traditional surrogacy, in which the patient donates her own egg, is not as successful as assisted reproductive technology but still offers favorable results.

Future fertility options

Without a doubt, preimplantation genetic diagnosis presents the most promise for cancer patients. The procedure allows genetic disorders to be diagnosed prior to implantation, allowing for prenatal testing for cancer susceptibility syndromes. Detection of abnormalities in 3-day-old embryos helps provide an understanding of the risks for recurrent pregnancy loss that some women experience. This procedure may reduce that risk and provide insight as to when donor embryos or oocytes may be beneficial. It also helps identify risk in breast cancer patients, as breast cancer ovarian syndrome susceptibility is directly linked to family history. Via biopsy, this genetic susceptibility can be identified early on, permitting patients to make informed decisions about conception.

Conclusion

Physicians are busy professionals with very limited time for communicating with other physicians, let alone collaborating. Nevertheless, the future of fertility preservation in cancer patients and their resulting quality of life rests in the hands of physicians who do make the time for communication and collaboration. Take time to talk to all sides involved to determine what benefits are available for cancer patients, then educate patients on these. When professional success is measured by the personal success of patients, collaboration becomes an imperative. Collaborate and share data. Continue to produce data that others can use. Continue to conduct research; the available data change every day. New technologies are developing daily, and these great changes are something in which we can all take part.