Use of GnRH Agonists in Female Cancer Patients

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In the year 2015, one in every 250 people in the United States will be a survivor of a childhood cancer.¹ This statistic is a strong testimony to the efficacy of many current cancer treatments. However, the majority of these patients will be unable to have children. Today, cancer survivors are increasingly concerned with late effects of these treatments/quality of life issues (including fertility) as they live beyond their diagnosis and treatment. In 2006, the American Society for Clinical Oncology (ASCO) published a set of guidelines regarding fertility preservation in cancer patients.² These guidelines stress that all cancer patients should be apprised of the effect of their proposed treatment on their fertility, be offered a comprehensive fertility preservation consultation, and have access to fertility preservation interventions before beginning cancer treatment. However, a recent survey indicated that only about a third of oncologists are aware of these guidelines, and that even fewer actually refer their patients for fertility preservation consultation.³

Background and Clinical Indications for Use of GnRH Agonists

Women are born with all the eggs (oocytes) that they will ever have during their lifetime and have no way to replenish them if they are lost. Any treatment that damages or destroys the ovarian reserve (the resting pool of oocytes in the ovary) will lead to loss of fertility and onset of early menopause. Cancer patients who undergo treatment with alkylating agents, radiation to the pelvis/induction chemotherapy for bone marrow or stem cell transplant are at high risk for loss of fertility because of a direct effect on the ovarian reserve.⁴ There are a variety of fertility preservation options available for female patients, including banking of eggs, embryos or ovarian tissue and even the use of donor eggs at a later date.⁵

The use of gonadotropin-releasing hormone (GnRH) agonists for fertility preservation has been widely reported in the oncology literature, however, studies showing that they are largely ineffective have been published in fertility journals. Oncologists must be made aware that 1) the use of GnRH agonists will likely not preserve fertility in their patients, 2) that patients should have access to in-depth fertility preservation consultation and intervention prior to the start of treatment and 3) that these interventions need not delay chemotherapy.

GnRH agonists, such as leuprolide acetate, Lupron Depot* (leuprolide acetate for depot suspension therapy) and Zoladex* (goserelin), are often used in cancer patients as an adjunct to chemotherapy and radiation. GnRH agonists are very effective in suppressing endocrine function (via a direct effect on the hypothalamic pituitary axis) and are widely used in hormone-sensitive tumors of the breast and prostate. Based on this mechanism of action, they are also often part of standard treatment protocols for young female patients undergoing chemotherapy and particularly induction treatment for bone marrow and stem cell transplants to control the heavy menstrual bleeding which these patients frequently experience. However, use of GnRH agonists for fertility preservation is on the rise, without any prospective randomized studies to support its efficacy for this indication. This practice may pose new challenges for many oncologists in terms of risk-management techniques.
GnRH Agonists and Loss of Fertility

Chemotherapeutic agents are designed to target rapidly-dividing cells. It has been postulated that quiescent cells may be less susceptible to chemotoxicity. The use of GnRH agonists to “shut down” the neuroendocrine access was theorized to protect the oocytes in the ovarian reserve. Despite GnRH agonists having no direct effect on the ovary, a number of studies have been published which purport to demonstrate that the use of these agents protects female fertility from the damaging effects of chemotherapy.6-9 These studies all suffer from the same limitations. First, they were largely carried out in patients who were receiving chemotherapy that would not be expected to compromise fertility, e.g., patients receiving doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) for lymphoma. Second, the endpoint of all these studies is return of menses following treatment, not return of fertility. There is no correlation between menses and fertility. For example, virtually all normal women on birth control pills and hormone replacement treatment post menopause will continue to menstruate despite the fact that they are not fertile. Finally, in studies where pituitary hormones, such as follicle-stimulating hormone (FSH) and anti-mullerian hormone (AMH), were measured, there was clear evidence of ovarian damage (as evidenced by elevated FSH and decreased AMH levels) in the face of normal menses. These studies report that there is no difference in fertility rates between patients who have received GnRH agonists with chemotherapy compared to control groups who received no GnRH agonists. The lack of difference between treated patients and controls clearly demonstrates a failure of fertoprotection.

Studies performed in vitro using human ovarian tissue also failed to show a protective effect using follicle number and hormone production as endpoints.10 In addition, a growing number of prospective studies have failed to show any protective effects of GnRH agonists using clinically relevant endpoints, such as FSH and AMH levels and return of fertility.11-14 Some clinicians would argue that the use of GnRH agonists “can’t hurt and might help.” However, this argument is also unsupported. GnRH agonists have a range of well-documented side effects. The most common of these are profound depression, sleep disturbances and vasomotor symptoms, none of which is welcome in a cancer patient. Since GnRH agonists suppress endocrine function, long-term treatment regimens—particularly in conjunction with corticosteroids—can lead to bone loss. These side effects are not inconceivable. The manufacturer package inserts can provide more information.

Furthermore, during the first seven to 10 days of GnRH agonist treatment, there is an initial flare of pituitary hormones that can lead to superovulation and enhanced fertility. Spontaneous pregnancies in this flare period are not uncommon—in fact, this effect is used to an advantage in patients being treated for infertility.15 Use of barrier contraceptive methods are imperative in this period to prevent unplanned pregnancies which may delay or complicate cancer treatment. However, contraception counseling is rarely part of the chemotherapy consultation.

Conclusions

In summary, use of GnRH agonists for fertility preservation is unsupported by prospective randomized studies. The studies that have appeared to show a fertoprotective effect were done in low-risk populations (patients receiving treatments with low risk for causing infertility) with endpoints that were not clinically meaningful, i.e., return of menses rather than pregnancy. These agents typically have side effects which can be problematic in the young cancer patient undergoing chemotherapy. These may include depression and bone loss. There are no studies that suggest that these agents would have any effect in patients receiving radiation treatment. There is no biological mechanism that would suggest that these agents would have a protective effect on fertility. The use of GnRH agonists should be undertaken with caution with an eye on the proven indications: removal of endocrine support and control of bleeding. All cancer patients should have the option of a comprehensive fertility preservation
consultation and be given access to fertility preservation interventions, including banking of sperm, eggs, embryos and ovarian tissue.

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About the author:
Marybeth Gerrity, PhD, MBA is currently the president and founder of RBR, Inc. where she has provided management consulting services to provider networks, clinical practices and specialty laboratories since 1983. She holds an MBA from the JL Kellogg Graduate School of Management at Northwestern University and both a PhD and MS in reproductive pharmacology from New York Medical College. Dr. Gerrity is board certified by the American Board of Bioanalysis as a high complexity laboratory director, embryology laboratory director and clinical consultant.

Most recently, Dr. Gerrity served as executive director of the Oncofertility Consortium, a nationwide, interdisciplinary and interprofessional group based at Northwestern University, Feinberg School of Medicine. This program is funded by the National Institutes of Health and is dedicated to the advancement of technologies that provide improved fertility-preserving options to patients with cancer and other chronic diseases. Over the past three years, the Oncofertility Consortium has established a network of 60 centers to provide comprehensive fertility preservation services and improve the quality of life for young cancer survivors.

Dr. Gerrity is also a practicing embryologist who was responsible for the world’s first in vitro triplets. She has established and directed a number of successful assisted reproductive technology programs and has served as consultant to over 150 others nationwide. She was an original author of the ASRM Guidelines for Embryology Laboratories and served on the ASRM/CAP Committee which developed the laboratory inspection checklist, standards, lab accreditation and proficiency testing programs that are still used to benchmark reproductive laboratories.

Dr. Gerrity is a frequent invited speaker in the areas of fertility preservation in patients with chronic diseases, risk management, tissue banking and quality improvement.

References


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