Ovarian stimulation for the female patient with estrogen-responsive disease

Glenn Schattman, MD, FACOG
Rodriq E. Stubbs, NP

In patients with a history of an estrogen-responsive tumor or for those diagnosed with an estrogen-responsive disease that has yet to be treated, ovarian stimulation presents the ultimate dilemma. Multiple eggs usually means high estrogen levels. The long-term side effects of chemotherapy or pelvic/abdominal radiation leading to ovarian senescence can be troubling to any patient. But to women who still want to have children, premature ovarian failure or loss of reproductive potential can be just as devastating as the life-threatening illness for which they are being treated. Preserving gametes and the potential for having biological offspring allows patients to better cope with their primary disease. It also provides the chance to focus on quality of life after cancer.

Depending on the type and dose of chemotherapy or the dose and location of radiation treatment, patients can expect varying degrees of reduction in reproductive competence.1 Treatments may have the effect of aging the ovaries by a few, or potentially, many years. This reduced fertility may be masked by persistent ovarian function and menstrual cycles. For women who wish to have children in the future, it is essential to explore fertility-preserving options before beginning any treatment that may affect reproductive potential.

To preserve future fertility, ovarian stimulation and oocyte retrieval with cryopreservation are typically performed prior to starting cancer treatment. This results in a limited number of stored gametes to be used if a patient experiences ovarian failure prior to completing her family. Many patients will not be infertile after cancer treatment, and some may be able to have children without medical intervention. However, these women will have a shortened reproductive lifespan due to chemotherapy’s effects on the ovaries, as mentioned above. These women may also need to delay conception for up to five years due to neoadjuvant hormone therapy, a wait that can further reduce the chances of pregnancy.

Limits of cryopreservation

Until recently, freezing eggs has had limited success. Improvements in cryoprotectant solutions and protocols have resulted in improved success rates for younger women who undergo the process with fresh eggs.2 And, while there has been a lot of press about vitrification (ultra-rapid chilling) for oocytes, optimized slow-freeze protocols have much less operator-dependent variability and similar success rates. Without question, however, any manipulation of the egg, including freezing, can potentially damage the oocyte and reduce the implantation potential of the resulting embryo.3

In addition, the effects of aging on reproductive efficiency cannot be emphasized enough. The percentage of abnormal eggs a woman produces rises exponentially with advancing age.4 Freezing these eggs, which are more sensitive to environmental perturbations, results in a significantly lower implantation potential despite improvements in freezing methods.5 Because many women presenting with estrogen-sensitive tumors are already in their later reproductive years and have reduced fertility potential, any eggs retrieved are more likely to be abnormal. The innate inefficiency of human reproduction, especially evident in later reproductive years, makes it imperative to maximize the number of gametes in the bank.

Ovarian stimulation as a safe option

Retrieving and cryopreserving as many eggs as possible prior to initiating chemotherapy is the goal of fertility...
preservation in this patient population. Unfortunately, options that do not involve ovarian stimulation, such as natural cycle *in vitro* fertilization (IVF), retrieve a limited number of gametes and do not provide a reasonable chance of pregnancy. Options that include some degree of follicle stimulation to retrieve multiple oocytes offer better chances for success, with the caveat of higher estrogen levels.

Patients with estrogen-responsive tumors are often concerned about the effects of the higher estrogen levels seen during ovarian stimulation. However, high estradiol levels with stimulation are only seen for approximately two weeks. In addition, increased estrogen levels occur after the patient has undergone surgical debulking of any tumors and before receiving medical treatment for any potential residual disease. Patients do not want to have to choose between an optimal cancer treatment outcome and having a child. Fortunately, there are a number of well-studied options as well as newer approaches for stimulating follicular development and improving oocyte yield without extremely elevated levels of estrogen.

Ovarian stimulation involves providing gonadotropins to the developing ovarian follicles at a level that is at or above the threshold for stimulating further growth of that follicle. The challenge is to administer just enough medication to initially recruit adequate numbers of follicles and support continued growth of the developing follicles, while preventing excess or delayed recruitment of additional follicles near the time of egg retrieval. The goal of increasing egg numbers through ovarian hyperstimulation should not come at the cost of egg quality and viability or a patient’s wellness. This physiologic stimulation approach, which has always been practiced at our center, is individualized for each patient based on her physiology and the sensitivity of her follicles to the gonadotropins. Through careful monitoring of blood levels and ultrasound examinations, it is possible to safely recruit the maximum number of follicles without compromising egg quality.

Even so, supraphysiologic levels of estradiol can occur, often four- to fivefold higher than peak natural cycle estradiol levels and sometimes greater than tenfold peak estradiol levels. However, these supraphysiologic levels typically last just two to three weeks and usually occur immediately prior to chemotherapy, which should treat any residual disease. In theory, ovarian stimulation and high estrogen levels might even improve outcomes in these patients prior to adjuvant treatment, as most chemotherapy targets tumor cells that are actively dividing. High estrogen levels might make the tumor cells more sensitive to the chemotherapy.

### Retrieval and *in vitro* maturation

Another option for this patient population is the retrieval of immature oocytes for cryopreservation and subsequent *in vitro* maturation or for maturation prior to cryopreservation. While not technically “*in vitro*” because the majority of the oocyte maturation occurs *in vivo*, these protocols allow for eggs to be collected earlier than with conventional ovarian stimulation protocols. Most protocols require the use of human chorionic gonadotropin (hCG) when the endometrium reaches a certain threshold thickness and the lead follicle is less than ~12 mm in diameter. Sometimes a truncated stimulation, with either follicle-stimulating hormone (FSH)/human menopausal gonadotropins (FSH + luteinizing hormone activity) along with hCG, can be given. Theoretically, in these patients who are not attempting to conceive in the same month as their oocyte retrieval, endometrial thickness is irrelevant. This type of cycle has been most studied in polycystic ovarian syndrome-like patients because they often have excess follicles. While this generally yields an increase in oocyte numbers over what would be retrieved in a natural cycle, this appears to come at the expense of egg quality, as demonstrated by reduced implantation rates. With respect to patients attempting to preserve their future reproductive options, this approach might not offer the best chance of achieving that goal.

### The role of SERMs and aromatase inhibitors

Ideally, any ovarian stimulation protocols used in this patient population should stimulate multiple follicles to develop while maintaining normal or low levels of estradiol. This can be accomplished either by blocking the estradiol receptor with a selective estrogen receptor modulator (SERM), like tamoxifen, or blocking the production of estradiol with an aromatase inhibitor, like letrozole, that prevents the testosterone from converting into estradiol. SERMs and aromatase inhibitors have shown promise as adjuvant treatments to reduce recurrence rates in patients with estrogen-responsive breast cancers. Clomiphene citrate and tamoxifen are two SERMs that have been used for many years to induce ovulation and treat estrogen-responsive breast cancers. Despite elevated levels of estradiol from multiple follicles, estradiol receptor inhibition in these patients is evidenced by compromised endometrial development.

Tamoxifen has been the most widely studied treatment for preventing recurrence in patients with estrogen-responsive breast cancer and, as such, has been the most widely used for ovulation induction in this group. In two separate
studies comparing natural cycle IVF to tamoxifen or tamoxifen in combination with FSH or letrozole in combination with FSH, neither natural cycle IVF nor tamoxifen alone resulted in the best outcomes. Both the tamoxifen with FSH and letrozole with FSH resulted in significant improvement in egg yield over tamoxifen alone, with 6.9 ± 1.1 and 11 ± 1.1 oocytes recovered, respectively (Figure 1).

Figure 1. Ovulation induction protocols

Yields may improve even more with newer regimens that allow for individualized dosing of the aromatase inhibitor and more conventional stimulation protocols already familiar to fertility specialists. One ongoing trial at our center comparing conventional, fixed-dose letrozole to a titrated dose of letrozole may yield even better methods of maximizing outcomes (Figure 2).

Figure 2. Titrated letrozole protocol

Conclusions

Once adequate time has passed to reduce the risk of recurrence and the effects of chemotherapy on remaining oocytes, patients can consider pregnancy. For many women recovering from cancer, potential pregnancy often raises renewed fears of elevated hormone levels and concerns about tumor resurgence. Patients with breast cancer can be reassured that in the many studies published to date, the evidence is overwhelmingly positive that there is no increased risk for recurrence with pregnancy after cancer. Some studies even demonstrate a reduced risk for recurrence of disease.

Patients who are facing breast cancer but wish to have children in the future should not despair. It is entirely possible to help these women by raising the issue of their future reproductive potential before the initiation of cytotoxic treatment. Even if the patient has not yet decided on a specific treatment plan, referring her to a reproductive specialist, providing her with information about how her treatment might affect reproductive potential and outlining options to preserve her future reproductive choices is of utmost importance.

Informed patients approach their treatments in a more positive manner, which can make difficult choices easier. Phone or office consultations to describe the “what if” scenarios can be especially helpful for patients at high risk of gonadal failure following treatment, those who are unsure of their options and even others whose risk of infertility following treatment is low. Patients who elect to pursue fertility preservation can do so with the knowledge that ovarian stimulation with an aromatase inhibitor or a SERM, along with individualized gonadotropin protocols, will significantly improve their long-term chances of having a biological child while minimizing adverse outcomes and improving treatment success.
About the author:

Glenn Schattman, MD, FACOG, is a specialist in infertility and reproductive surgery at the Center for Reproductive Medicine and Infertility at the Weill Cornell Medical College at New York-Presbyterian Hospital. He is board certified in obstetrics and gynecology with subspecialty board certification in reproductive endocrinology and infertility. He is an associate professor of obstetrics and gynecology at the Weill Cornell Medical College at New York-Presbyterian Hospital.

A leading figure in fertility preservation and the correction of common causes of infertility, Dr. Schattman is directing a number of ongoing research studies designed to improve outcomes for women facing the prospect of infertility due to cancer treatments. He uses minimally invasive surgical techniques and is a pioneer in the use of robotic surgeries for procedures that would normally require open surgery, including fibroids and tubal ligation reversal.

Dr. Schattman received his medical degree from the State University of New York, Downstate Medical Center in Brooklyn, New York in 1987. He completed his residency at the George Washington University Medical Center in Washington, DC in 1991, and finished his fellowship in reproductive endocrinology and infertility at the New York Hospital/Cornell University Medical College. He is president-elect of the Society for Assisted Reproductive Technology and is a member of several other medical associations. An author of numerous articles and manuscript chapters, Dr. Schattman also lectures internationally on a wide range of topics.

References