

## PRESERVING REPRODUCTIVE OPTIONS IN ONCOLOGY PATIENTS

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### **Introduction**

Over the last several decades we have witnessed a significant increase in survival rates for oncology patients. Due to the use of combination chemotherapy and radiotherapy many young patients are now living long healthy productive lives. While combination regimens have been designed to avoid acute toxic effects, many have resulted in unanticipated gonadal toxicity. As such, an increasing number of cancer survivors are now facing difficulties in having families as well as hormonal deficiencies.

### **Preservation of Reproductive Options in Men**

Gonadotoxicity in males is dependent on the stage of spermatogenesis affected. Damage to mature sperm with sparing of the stem cells will result in a temporary diminishment of spermatogenesis, while damage to the stem cells will result in permanent impairment of spermatogenesis. The simplest option in males is cryopreservation of sperm prior to the initiation of treatment. There is a long history that demonstrates both the efficacy and safety of utilizing cryopreserved sperm. The risk of transmitting a malignancy to either his partner or to the offspring is negligible. The incidence of abnormalities in the children in women who recover their ovarian function after chemotherapy or to men who father children after treatment has been reviewed in over five hundred cases and there appears to be no increase in still births, fetal abnormalities and spontaneous abortion rates.

There are now a number of recent advances that have greatly expanded options in men who have already undergone treatment. The ability to retrieve sperm via epididymal or testicular aspiration is able to be performed in the office with minimal discomfort and may result in the retrieval of sperm in those who are presumed to be azoospermic by semen analysis. Coupled with intracytoplasmic sperm injection (the injection of sperm into the oocyte) this has tremendously expanded reproductive options in these couples. Unfortunately, preliminary evidence suggests that the use of GnRH agonist/antagonists are not effective in minimizing the cytotoxicity of chemotherapy to the gonads and thus there is little that can be done to minimize gonadotoxicity once treatment has been initiated.

### **Preservation of Reproductive Options in Women**

In women, many cancers directly affect reproduction and childbearing functions thereby causing severe difficulties and distress. Unfortunately, the preservation of fertility is much more complex in women. First, radiation can adversely impact the uterus by either directly compromising the endometrium or indirectly by reducing its blood flow. Second, both radiotherapy and chemotherapy may directly impair germ cell function. Unlike men, women possess a finite number of germ cells at birth and diminish with age.

With cytotoxic therapy, the rate at which primordial follicles regress is greatly accelerated. A variety of approaches have been utilized in order to preserve either oocytes or ovarian tissue. Until recently, attempts to cryopreserve unfertilized oocytes have not yielded satisfactory results. Two approaches have been taken in preserving unfertilized eggs. The first utilizes immature oocytes (eggs that are extracted prior to complete maturation). The obvious advantage is that it allows for the extraction of multiple oocytes at anytime during follicular maturation. Unfortunately, at this time the technology is in its early stages of development and is not clinically applicable. Excitingly, the ability to preserve and utilize mature oocytes is emerging as a viable option.

Research currently being performed at Huntington Reproductive Center and a select number of programs has demonstrated the feasibility of this technology. The ability to preserve unfertilized oocytes is significant because it allows single women to cryopreserve their eggs without having to fertilize them first. The down side to this technology is that it requires patients to undergo ovulation induction prior to retrieving their oocytes. This may result in an unacceptable delay in the initiation of cancer therapy.

More recently, several labs have looked at the versatility of preserving ovarian cortical stripes. The advantage of ovarian cryopreservation is that each biopsy allows for the preservation of thousands of oocytes in their natural environment. While there are only a handful of patients who have undergone this procedure, preliminary results are promising. There are now several cases of women who have undergone successful transplantation of tissue with subsequent preservation of endocrine function. Successful ovulation induction with oocyte aspiration from ovarian tissue transplanted under the forearm has been performed. Unfortunately, this procedure has yet to result in a pregnancy and the potential of transplanting microscopic nests of tumor cells exist.

Nonetheless, cryopreservation of ovarian tissue shows promise. Embryo cryopreservation, fortunately, has been successfully performed since 1983 and has resulted in thousands of offspring. In more successful labs, pregnancy rates in frozen embryo transfer cycles are similar to fresh embryo transfers. This allows women to complete their cancer treatment with subsequent initiation of childbearing at a future date. Several drawbacks exist, however. Most choosing embryo cryopreservation must undergo ovulation induction with subsequent oocyte aspiration. This may result in an unacceptable delay in the initiation of treatment. Furthermore, embryo cryopreservation is not an acceptable alternative in children and may not be an acceptable option in single women.

In women undergoing radiotherapy to the pelvis, the ovaries are frequently exposed to unnecessary doses of ionizing radiation. While the exposure may not result in premature ovarian failure, the impact frequently results in suboptimal endocrine function and infertility secondary to the cytotoxic effect on the oocyte. Several strategies have been devised to minimize damage to the ovaries. First, in patients receiving external beam brachytherapy, a skilled radiation oncologist may be able to minimize unnecessary

ovarian exposure through careful positioning and use of padding. Second, the ovaries can be transposed out of the pelvis surgically. This can be accomplished laparoscopically by fixing the ovary to the psoas muscle. This can be accomplished as an outpatient procedure with minimal discomfort to the patient and should not delay therapy. As the uterus cannot be spared from the effects of radiation, it is advisable that these women have surrogate carriers when initiating childbearing.

It has been recognized that girls undergoing chemotherapy prior to the onset of menses with alkylating agents have significantly improved ovarian endocrine and reproductive function compared to those receiving similar therapy after menarche. Pre and concomitant treatment with GnRH analogs appears to be the most promising approach to prevent ovarian failure induced by chemotherapy. There is a growing body of evidence that suggests the analogs minimize the gonadotoxic effect of chemotherapy by inducing a temporary prepubertal state. GnRH inhibits the process of follicular recruitment and thus inhibits follicular maturation. Thus, it appears that GnRHa prevents the follicles from reaching the chemo-sensitive stage via suppression of the granulosa cells.

As the agonists take 2-3 weeks to suppress follicular recruitment, therapy should be started prior to the initiation of chemotherapy. It is unclear whether GnRH antagonists convey the same protective benefit. Theoretically, one would expect a similar protective effect. The antagonists have the benefit of immediate suppressive effect and thus would not require pretreatment. Interestingly, a similar gonadoprotective effect is not seen in males.

### **Ethical Dilemmas**

There are a number of ethical dilemmas that must be answered while addressing this issue. While it is beyond the scope of this paper to discuss this in detail, I have listed a number of concerns. To whom do we offer treatment? Do we consider harvesting and preserving gonadal tissues in children and adolescents? What about poor prognostic candidates? Is it acceptable to delay or compromise treatment in order to maximize future fertility?

### **Conclusions**

Given the tremendous strides made in both the fields of oncology and reproductive endocrinology, future reproductive considerations must be addressed in individuals undergoing cancer therapy. Embryo and oocyte cryopreservation and potentially ovarian tissue cryopreservation (the only alternative for prepubertal girls) should be utilized when appropriate. Lastly, GnRHa/chemotherapy co treatment should be offered when patients are at risk of gonadotoxicity.