

Oncofertility: The Preservation of Fertility Options for Young People with Cancer

Teresa K. Woodruff, Ph.D.

The Thomas J. Watkins Professor of Obstetrics and Gynecology, The Feinberg School of Medicine, Northwestern University, Chicago, IL

Cancer is now a disease with a variety of treatment options, which are leading to longer and more productive lives by survivors. Globally, there are 10 million people diagnosed with cancer. 10% of these newly diagnosed men and women are under the age of 45 years old. Infertility can be a consequence of many of the more aggressive chemo- and radiation therapies that prolong and save lives. The ability to easily preserve sperm prior to cancer treatment provides hope at the time of diagnosis and families later in life for male survivors. A notable example is Tour de France winner Lance Armstrong who has three children conceived using sperm frozen days before he underwent the massive chemo- and radiation therapy that saved his life. Unlike sperm, the female germ cell, the oocyte or egg must be retrieved surgically. Moreover, the vast majority of collected oocytes will be immature and cannot be used immediately by a woman who is ready to start a family. The *overall hypothesis of the program* is that effective fertility-extending options can be provided to young women undergoing life-preserving cancer treatment. The purpose of our work is to bring physicians, medical ethicists, social scientists and basic scientists together to develop new strategies for fertility preservation for female cancer survivors under the new discipline of *oncofertility*. And even as the lexicon is being established, complex bioethical issues face both providers and parents. At the basic science level, complex issues of ovarian function and preservation must be addressed including the problem of follicle growth and development *in vitro*. Our investigative group has pioneered the development of a 3-dimensional system that supports follicle development, largely, we believe, because the links between the egg and its surrounding cells are maintained. Using a tissue-engineered approach, we have developed an *in vitro* follicle growth system that supports the maturation of the enclosed oocyte, which can be fertilized and results in live, healthy and reproductively competent mice. The goal of our program and the broader Oncofertility Consortium is to explore and expand the reproductive options available to young people facing a fertility-threatening but life-preserving cancer treatment.

This work is supported by NIH/NICHD Structure-Function Relationships in Reproductive Science, U54 HD041857; and, the Oncofertility Consortium, UL1DE019587 and RL1HD058295

Oocyte in vitro maturation and cryopreservation for fertility preservation

Ariel Revel, MD.

Hadassa Medical Center Jerusalem

Fertility preservation has been an area of interest for many years. The ability to have a biological child is the goal of the vast majority of mankind. The development of slow freezing methods has managed to decrease the ice formation and is used clinically to save sperm and embryos. Until recently, the possibility to freeze non fertilized oocytes was not realistic due to the poor clinical results obtained after thawing. The introduction of vitrification has presented a revolution in this situation. Thus, oocytes that were vitrified and thawed can be considered as having almost the same potential as fresh oocytes.

Since the most significant enemy of women ovarian function is her age, it is logical that women find these new technologies to be interesting to bank their oocytes. Thus, female fertility preservation has moved from offering this to young patients facing gonadotoxic chemotherapy to offering it to all women. The social, psychological, ethical and financial implications of this approach should be discussed.

How to Preserve Fertility in Young Women Exposed to Chemotherapy? The Role of GnRH-a in addition to Cryopreservation of Embrya, Oocytes, or Ovaries

Zeev Blumenfeld, M.D.

*Reproductive Endocrinology, OB/GYN, Rambam Health Care campus, Technion-Faculty of
Medicine, Haifa*

Preservation of fertility despite chemotherapy has gained ubiquitous worldwide interest. In a prospective randomized study, GnRH-a protected the ovary against cyclophosphamide-induced damage in Rhesus monkeys. We have administered GnRH-agonist to more than 160 young patients exposed to gonadotoxic chemotherapy, for up to six months. Less than 7% developed irreversible hypergonadotropic amenorrhea and premature ovarian failure [POF]. The remaining patients (>93%) resumed cyclic ovarian function, and 37 patients spontaneously conceived 50 times. A control group of over 130 patients of comparable age (15-40) were similarly treated with chemotherapy without the GnRH-a. Neither the age, nor the diagnoses, radiotherapy exposure, cumulative doses of each chemotherapeutic agent differed between the groups. The GnRH-a prevents the thrombocytopenia associated menometrorrhagia and anemia in these patients. GnRH-a administration is also effective in patients receiving cyclophosphamide pulses for SLE and other autoimmune diseases. Recently we have experienced the first worldwide reported case of two spontaneous successful deliveries of two healthy neonates after TWO repeated BMT's, treated with GnRH-a during gonadotoxic chemotherapy. In a recent prospective randomized study, GnRH-a was shown to significantly protect the ovary against chemotherapy-associated POF in young women with breast cancer. Several explanations may be put forward to explain the beneficial effect of the GnRH-a:

- I. GnRH-a simulates the prepubertal hormonal milieu.
- II. Decrease in the utero-ovarian perfusion, secondary to hypoestrogenism.
- III. Direct effect of GnRH-a, independent of the hypogonadotropic milieu.
- IV. Up regulation of an intragonadal antiapoptotic molecule such as sphingosine-1-phosphate (S-1-P), which has been shown to prevent chemotherapy induced gonadotoxicity both *in-vivo* and *in-vitro*.
- V. Possible protection of an undifferentiated germinal stem cell.

Recently a prospective randomized study has validated the protective role of GnRH-a in preservation of ovarian function despite chemotherapy in young women with breast cancer.

The administration of GnRH-a should be considered and offered to every young woman before chemotherapy, in addition to cryopreservation of embrya, oocytes, or ovaries.

AMH as a predictor of ovarian reserve

Dr. Hannah Kanety, Ph.D

Institute of Endocrinology, Sheba Med. Ctr. Tel-Hashomer.

Anti-Müllerian hormone (AMH) is a dimeric glycoprotein, a member of the transforming growth factor (TGF) superfamily. It is produced by ovarian granulosa cells and is involved in the regulation of follicular growth and development. As AMH is largely expressed throughout folliculogenesis, from the primary follicular stage towards the antral stage, serum levels of AMH may represent both the quantity and quality of the ovarian follicle pool. Indeed, serum AMH level correlates with ovarian follicle number. Compared to other ovarian tests, AMH seems to be the best marker reflecting the decline of ovarian reserve. No significant changes in AMH levels occur throughout the menstrual cycle; therefore, AMH is a reliable marker at any time during the menstrual cycle in contrast to current practice day 3 FSH.

AMH represents a useful clinical marker for the assessment of ovarian reserve in cases of subfertility caused by advanced age in women. It can also be used to predict poor ovarian response of *in vitro* fertilization (IVF) cycles. AMH has been shown to be a good surrogate marker for polycystic ovary syndrome (PCOS). In addition, AMH levels are useful for monitoring ovarian reserve in cancer patients both pre- and post- chemotherapy, which is known to often reduce ovarian reserve. Testing AMH levels before chemotherapy may allow more informed personal decisions about egg banking or timing of child bearing. AMH has also been shown to be useful in granulosa cell tumor detection and therapy monitoring.

In conclusion, AMH measurement may be a useful tool for clinicians in the field of reproductive medicine.