Teacher Background

Fertility Preservation Options for Cancer Patients

Note: The Teacher Background Section is meant to provide information for the teacher about the topic and is tied very closely to the PowerPoint slide show. For greater understanding, the teacher may want to play the slide show as he/she reads the background section. For the students, the slide show can be used in its entirety or can be edited as necessary for a given class.

What is Oncofertility and why is it important?

Oncofertility is a new approach in medicine for working with cancer patients under 40 years old. It encompasses comprehensive medical approaches to preserving fertility in these patients before their cancer treatment begins. Due to improvements in cancer treatments, by 2015 , 1 person in 285 will be a diagnosed with childhood cancer before the age of 20 and more than 80% of those people will survive 5 years or more after their diagnosis. (1) This success is often the result of timely and aggressive treatment for the disease. However, this approach has consequences that are coming to light as the treatments become more and more successful. Radiation therapy and some chemotherapy treatments for cancer can destroy the sperm-forming germ cells and existing oocytes which are present at birth. The new field of oncofertility promotes an early meeting between the oncologist, the patient, and a fertility specialist when cancer patients are under the age of 40, so that fertility options can be discussed prior to the onset of treatment.

What are some methods of fertility preservation and why are they different for males and for females?

One method of fertility preservation is to freeze the patient's embryo, sperm or oocytes (eggs) in liquid nitrogen prior to the cancer treatment. Embryos and sperm have been successfully frozen and thawed for many years, a process that has resulted in millions of live births. Oocytes are a different matter, however, since the oocyte is much larger than a sperm cell and contains much more water. When water freezes, ice crystals form and these crystals are very damaging to the structures inside the oocyte. Comparatively few live births have resulted from frozen and thawed oocytes. Furthermore, whereas the production of sperm continues throughout the life of a male, the number of oocytes is finite. The oocyte

resides in a follicle until the follicle is mature and can ovulate or burst open, thus releasing the oocyte. A mature oocyte is released from an ovary during the monthly cycle in post-pubertal females. In addition to freezing sperm and oocytes, tissue from testes and ovaries can be harvested and frozen. This would be especially important for preserving fertility in prepubertal children, adolescents and young adults who will be undergoing chemotherapy and/or radiation therapy.

What are goals and novel strategies for preserving fertility in female patients?

The goals of fertility preservation in females are to understand the fundamentals of follicle development, develop methods to mature follicles *in vitro*, and to provide germline preservation as an option for female cancer patients, NASA deep space astronauts, and endangered and threatened species. Novel strategies for bioengineering fertility preservation would include: a) ovarian protection, b) follicle culture, c) ovarian autografts, and d) cryopreservation (See Chapter 9, Cryobiology).

a) In order to **protect ovaries** from radiation and chemotherapy, experiments were conducted to see if applying intra-ovarian sphingosine-1-phosphate (S1P) to the ovary *in vivo* before X-irradiation of the pelvis would protect the follicles in the ovary from damage, thus preserving ovarian function.

   Background: In the ovary and other places in the body, a substance called ceramide acts in the programmed cell death pathway in response to stress kinases; this can lead to production of sphingosine and sphingosine1-phosphate (S1P) which prevents apoptosis. S1P was found to inhibit doxorubicin (chemotherapy)-induced oocyte death *in vitro*. Those oocytes that lack the enzyme sphinogomyelinase (which catalyzes the formation of ceramide) are resistant to doxorubicin-induced apoptosis *in vitro*. S1P was known to have a protective effect in mice and then it was tested in rhesus macaques. When S1P was used to surround the ovaries of monkeys as they were X-irradiated (radiation therapy), it was found to inhibit ceramide promoted apoptosis in the oocytes that were exposed to the radiation. (2)

b) In order to **culture follicles**, it is necessary to develop a scaffolding to contain the follicle with its oocyte while it matures. Follicles are 3-dimensional spheres and will collapse if not given scaffolding. Alginate, a material derived from large brown algae such as *Macrocystis* (such as giant bladder kelp), *Nereocystis* (such bullwhip kelp), and *Laminaria* (such as Devil's apron) has been effectively used to provide such a scaffolding for follicle maturation *in vitro.*

   Alginate is composed of polymers of two monomers, β-D-mannuronic acid and α-L-guluronic acid. The former polymer is called an M block and the latter is called a G block because of their distinctive ring structures. An alginate molecule is a polymer or long chain of M, G, and MG

monomers bonded together. When there is a high proportion of G blocks in the molecule, calcium salts, such as calcium chloride, can be added to form a strong gelatinous hydrogel of calcium alginate. This hydrogel is composed of one or more polymers suspended in water by crosslinking two or more of these molecules with covalent bonding.

When the hydrogel is made, a follicle with an oocyte in it can be placed into the gelatinous sphere which will support it structurally while the follicle continues to mature and grow. The strength of the gel depends on several factors, including the concentration of the alginate, the species of the alginate, its degree of polymerization, and the calcium concentration. A solution of 0.5% sodium alginate is the percentage used in many research labs for follicle scaffolding. When the Ca^{2+} is added, it makes a sphere that is not too stiff and not too fluid. (3)

The idea of the 3-dimensional nature of the follicle can be shown using seeds and nuts – a mature mouse antral follicle is about the size of a sunflower seed, a mature monkey antral follicle is about the size of a pistachio, and a mature human antral follicle is about the size of a pecan. When the antral follicle is fully matured, it can take up most of the ovary. If a thawed follicle is placed in an alginate bead, it will need to have hormones, such as FSH and LH, added to begin to grow. Another bioengineering task is how to construct alginate beads that are progressively larger and larger into which to transfer the follicle as it grows.

c) Using fresh **ovarian auto-grafts** in 2004, Dr. Wolf, Dr. Yeoman, and Dr. Lee at ONPRC were are to transplant fresh (non-frozen) ovarian grafts in the arm and abdomen of monkeys and produce a live birth from oocytes retrieved from that grafted tissue that were fertilized in vitro and the embryo transferred to a surrogate mother monkey. The tissue graft developed a blood supply and estrogen and progesterone were produced by the graft in higher amounts than were found in the circulating blood nearby. Oocytes collected from the ovulating graft tissue produced a live offspring named Brenda. (4)

Humans have also given birth after receiving small grafts of ovarian tissue. In 2008, a human baby was born in London after her mother naturally conceived after receiving a transplanted ovary from her twin. Cryopreserved tissue grafts are still considered an experimental treatment, although many live human births have resulted giving promise to this as an option for fertility preservation. (5)

d) Cryopreservation - See Chapter 8, Cryobiology

Much research is continuing to be done to help cancer patients preserve their fertility. It is also offering new hope to couples who are having difficulty getting pregnant.

Bibliography

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