KNOW BEFORE YOU GO

The best time for fertility preservation is prior to initiating chemotherapy or radiation.

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Hundreds of thousands of women in the United States are diagnosed with cancer each year. Many of these women are in their reproductive years and have not yet started or completed their families. Young women with cancer are increasingly surviving their disease because of improved treatment and earlier detection. While chemotherapy, a mainstay of cancer treatment, has decreased recurrences and improved survival, these medications also induce ovarian damage and aging, resulting in premature ovarian failure, infertility, and early menopause in cancer survivors. Though the potential for infertility is known to be a great source of stress for female cancer survivors, it can get lost in the whirlwind of emotions as a young woman faces her diagnosis of cancer; and because timely initiation of chemotherapy is an essential element to improving survival, many times fertility concerns are placed on the back burner and addressed only after chemotherapy or other cancer treatments are completed. It is important to understand, however, that the best time for fertility preservation is clearly *prior* to initiating chemotherapy or radiation. Here are some reasons why.

Chemotherapy and radiation reduce egg quantity.

It is known that chemotherapy and radiation to the pelvis can dramatically reduce a woman's supply of eggs. This can lead to premature menopause, and even those who resume or maintain regular menstrual cycles after chemotherapy may suffer infertility due to a reduced egg supply. Particularly at risk are women receiving higher doses of radiation and/or chemotherapy and certain types of chemotherapy (such as alkylating agents) and those who are older than 35 at the time of treatment. Because it is not possible to predict the impact that cancer therapy will have on an individual woman's egg supply, it is important to consider preserving fertility while there are still adequate numbers of eggs remaining.

The standard fertility preservation method is *embryo cryopreservation*, though *oocyte cryopreservation* may also be considered. For either method the process is similar to that of in vitro fertilization (IVF) in that it involves ovarian stimulation with daily injectable hormones for approximately 10 to 14 days to achieve multiple eggs.

One of the key elements of achieving success with IVF, embryo freezing, or egg freezing is the ability to stimulate and retrieve multiple eggs. Based on decades of clinical experience with IVF and frozen embryos, it is clear that having multiple embryos to transfer increases the chance of future pregnancy. Because each individual embryo has only a relatively small chance of implanting, or "sticking," in general the more embryos you have, the better.

Live birth rates from frozen-thawed embryos depend on the age of the woman at the time of the egg retrieval, ranging from approximately 30 to 40 percent per transfer for women younger than 35 years, to 10 to 20 percent per transfer for women between 41 and 42, assuming there are multiple embryos to transfer.

Data from women whose average age was 33 at the time of egg freezing suggest that approximately 5 percent of thawed eggs will successfully implant and 4 percent will result in a live birth. Thus approximately 20 to 25 eggs would need to be thawed to achieve a single live birth, and freezing 10 to 12 eggs would be expected to yield about a 50 percent cumulative chance of a live birth. One can assume that the older a woman is at the time of oocyte cryopreservation, the lower the probability of a live birth in the future.

Though some women do consider embryo or egg freezing after completion of their chemotherapy or radiation, the response to the ovarian stimulation is nearly always diminished, resulting in fewer eggs or embryos to freeze and a lower chance of pregnancy in the future. Thus to optimize the quantity of eggs produced and the chance of pregnancy, fertility preservation procedures are best done prior to initiation of chemotherapy or pelvic irradiation.

The effect of chemotherapy and radiation on egg quality is unknown.

The concept of a woman's "egg quality" is derived from the observation that the probability of an embryo's implanting is strongly related to the age of the woman who provides the egg and to her overall egg supply. Therefore "egg quality" is synonymous with "the probability of embryo implantation." The quality of an egg cannot be determined by looking at it or its resulting embryo. Just because an embryo looks good in the laboratory does not mean that it will implant. The only proof of good egg quality is in the embryo actually implanting.

One way to think of diminished egg quality is "the battery theory of aging." Consider each egg as possessing a number of batteries that provide its energy. The batteries represent tiny organs in all of our bodies' cells called *mitochondria*, which provide the energy for our cells to function. As we grow older, the energy-producing capacity of the mitochondria decreases. The egg is packed with mitochondria because it requires huge amounts of energy to drive the processes of fertilization, embryo growth, and implantation. The older egg usually looks normal at the time of ovulation, and its initial fertilization and embryonic development remain normal. This is because its energy stores are still adequate. It soon runs out of batteries, however, and the embryo stops growing. Implantation is not achieved because the embryo stops growing before it reaches the implantation stage.

As women age, the quantity of eggs decreases and the quality of eggs declines along with it.

This is the reason why the probability of embryo implantation decreases as a woman ages. While it is known that chemotherapy and pelvic radiation can reduce egg quantity in women with cancer, the effect on egg quality remains largely unknown. Though some women do consider embryo or egg freezing after completion of their chemotherapy or radiation, and many of them do produce eggs and embryos to freeze, the quality of the eggs after exposure to cancer therapy is not known. Thus to avoid potential effects of cancer therapy on egg quality, the best time for fertility preservation is before the initiation of chemotherapy or radiation (particularly in the region of the pelvis).