Horizons in Bioscience
FASEB

How Biomedical Research Provides Fertility Hope to Cancer Survivors

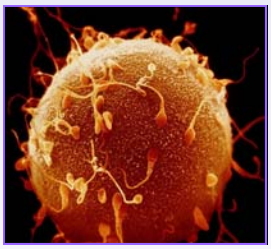
The process of reproduction has fascinated humans since ancient times. Hippocrates and Aristotle offered theories on conception and fertility, but it was not until the late 17th century that a Dutch scientist named Niels Stensen, who was studying the reproductive organs of animals, suggested that human ovaries might contain egg cells, or oocytes. Over a century later, this was definitively confirmed by one of the founding fathers of embryology, Carl Ernst von Baer.

Thanks to centuries of scientific research, we now know the details of how oocytes interact with sperm inside the reproductive tract to form the early embryo and ultimately new offspring. This understanding has led to the development of extraordinary treatments for infertility, from *in vitro* fertilization (IVF) to the cryopreservation (freezing) of embryos.

Did You Know?

- Oocytes and sperm are both known as *gametes*, which comes from an ancient Greek word meaning "husband" or "wife."
- Fertilization, the combination of the sperm and the oocyte, takes place in the organ called the Fallopian tube or oviduct.
- The term *in vitro* is Latin for "within glass." In the case of *in vitro* fertilization (IVF), this referred to the glass Petri dishes where sperm and oocytes were combined. Today, IVF takes place in specialized dishes made out of plastic, not glass.
- Much of our early understanding of embryo development came from studying the embryos of frogs, sea urchins, and newts. One species in particular, the African clawed frog (*Xenopus laevis*), ovulates easily when injected with the hormones produced during pregnancy (and was even used for pregnancy tests in the 1940s and 50s!), and produces large, easy to study embryos. *Xenopus* remains an important model for the study of embryo development.

But what if you're a woman whose lifesaving cancer treatment might make you unable to conceive children?



Anything that can damage oocytes, such as radiation treatments or chemotherapy for cancer, can affect fertility. For women and girls fighting cancer, this can be a devastating side effect of cancer therapy. Fortunately, breakthroughs in biomedical research provide new hope. Scientists are discovering ways to preserve ovarian tissue (where oocytes are formed and mature) and even grow a patient's own oocytes outside of the ovary.

These amazing breakthroughs, funded by the National Institutes of Health (NIH), are only the most recent chapter in a tale of discovery and medical advancement. Centuries of curious scientists, serendipity, and growing knowledge of human and animal reproduction have brought us to the brink of new treatments to preserve fertility in cancer patients.

History of IVF: A Rabbit of a Different Color

The first documented attempt to fertilize an oocyte with sperm outside of the reproductive system, using guinea pig gametes, was published in 1878. This early effort at *in vitro* fertilization was unsuccessful. In fact, nearly 100 years passed before a scientist named M.C. Chang was able to show that IVF could produce healthy babies by implanting embryos created by IVF into the uterus of a rabbit. The rabbit gave birth to a litter whose coat color resembled the rabbits that donated the eggs and sperm, rather than her own. This landmark study was quickly followed by similar results in mice, hamsters, sheep, dogs, and a wide variety of other species.

Why did it take so long for IVF to work? It turns out that reproduction is pretty complicated. Oocytes and sperm undergo a number of changes as they move through and mature in the reproductive system. Scientists first had to understand all of the steps in the process of fertilization and how to recreate them *in vitro*, as well as how to create an environment that mimicked the inside of the female reproductive tract.

Horizons in Bioscience is a product of the Federation of American Societies for Experimental Biology (FASEB) and describes scientific discoveries on the brink of clinical application. These one page documents are intended to supplement our longer series of illustrated articles, *Breakthroughs in Bioscience*; free hardcopies may be ordered and electronic versions of the full series may be found on our website: www.faseb.org

One Day Treatments To End Cancer Won't Mean An End to Fertility: New Research, New Discoveries, New Hope

Some female cancer patients may be able to create embryos through IVF and freeze them for later use before undergoing cancer therapies. But what if that is not an option?

Researchers have already developed experimental ways to freeze ovaries or ovarian tissue, store them until after cancer treatment is completed, and then re-implant them into a woman's body when she's ready to become pregnant. But this may not be the best option for all patients, because it's possible that some cancer cells may remain in the ovarian tissue and could cause new cancer to emerge.

However, scientists Teresa Woodruff, Lonnie Shea, and colleagues at Northwestern University have already made exciting advances in removing follicles, the tiny sacs in which oocytes develop, and maturing undeveloped eggs in the lab. This is the first critical step in oncofertility, preserving a woman's fertility following cancer treatment. Next, scientists will have to figure out how to push the oocyte to the final stage of development, in which it loses half its genetic material to make it ready to combine with the genes of the sperm. Finally, researchers need to show that human follicles can be stored in a freezer, thawed, and still used to grow eggs.

Like the scientists on whose foundation of knowledge they are building, today's researchers will continue to pursue the breakthrough discoveries that lead to the next generation of fertility advancements.

From Hamsters to Humans

One of the greatest challenges facing scientists in developing IVF systems was how to create an environment in a dish that could impersonate the reproductive system, fostering all the changes that the sperm and egg needed to undergo for successful fertilization. From 1954 onward, scientists made tremendous strides in perfecting these environments for a wide variety of species. But would any of them work for humans?

Miriam Menkin, a biologist and lab technician at the Free Hospital for Women in Massachusetts, became the first person to witness human fertilization outside the body when she successfully performed the first human IVF in 1944. Although she and her mentor, John Rock, went on to pursue other avenues, the quest for a human IVF system continued. In the early 1960s, a young Japanese scientist came to work in the lab of M.C. Chang, the researcher whose rabbits proved to the world that IVF could produce healthy babies. Chang's trainee, Ryuozo Yanagimachi, soon followed in his mentor's groundbreaking footsteps. Yanagimachi developed an IVF method in hamsters that would later go on to be used for the first human IVF system. The first human baby conceived through IVF, Louise Brown, was born on July 25, 1978. In 2006, she gave birth to her first child through natural conception.

"Hamster IVF paved the way for human IVF." -*Barry D. Bavister, Ph.D.,* Reproductive biologist

The Dawn of Cryopreservation

Cryopreservation is the name for freezing and storing cells and tissues. For centuries, scientists had tried to preserve sperm by freezing for use in artificial insemination, with little success. Freezing is hard on tissue: ice crystals form rapidly from water inside and outside the cells, causing damage to vital cell functions, and dehydration can occur. Researchers began to search for cryoprotective substances that would prevent this damage.

Although most scientific breakthroughs are built on decades of incremental discovery, the solution to cryopreservation was discovered entirely by serendipity. While searching for a cryoprotectant, Christopher Polge, a scientist in the United Kingdom, accidentally added glycerol to his experiment. To his surprise, the cells survived. The breakthrough discoveries of glycerol and subsequent cryoprotectants have made the freezing of sperm and embryos common parts of infertility treatments. (Interestingly, a student of Polge's named Ian Wilmut would go on to achieve his own fame through serendipity. After accidentally thawing an incorrect vial of cells, Wilmut decided to proceed with his experiment despite the mistake. That experiment resulted in the first mammal produced through reproductive cloning: Dolly the sheep, born in 1996.)

Oocytes which are large and filled with liquid, are much more susceptible to damage by freezing, and therefore seldom survive cryopreservation, even with the use of cryoprotectants. This leaves fewer options for female patients who may be undergoing cancer treatments that affect fertility.

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