

Ooplasmic Transfer Technology

Ooplasmic transfer, also called cytoplasmic transfer, is an outside the body, in vitro fertilization (IVF) technique. Ooplasmic transfer in humans (*Homo sapiens*) is similar to in vitro fertilization (IVF), with a few additions. IVF is the process in which doctors manually combine an egg and sperm cells in a laboratory dish, as opposed to artificial insemination, which takes place in the female's body. For ooplasmic transfer, doctors withdraw cytoplasm from a donor's oocyte, and then they inject that cytoplasm with sperm into a patient's oocyte. Doctors perform ooplasmic transfer to replace mitochondria that have genetic defects, which can cause a variety of disorders. In 1982, Audrey Muggleton-Harris's group at MRC Laboratory Animals Center in Surrey, United Kingdom, developed the technique and reported the first successful mammalian ooplasmic transfer in mice (*Mus musculus*).

In established IVF procedures, the female is stimulated with hormone injections to induce egg cell or oocyte production. A physician monitors the female for development of oocytes in her ovaries and collects the mature oocytes. After securing sperm cells, fertilization occurs by placing the oocyte and sperm together in a fluid medium or by injecting the sperm into the oocyte, through a technique called intracytoplasmic sperm injection. Doctors transfer the pre-embryo to the female's uterus after fertilization and after the pre-embryo shows the ability to grow. In ooplasmic transfer, doctors stimulate a patient and an ooplasm donor with hormone injections at the same time. They then harvest the patient's and donor's mature oocytes also at the same time.

Most mammalian fertilized oocytes (zygotes), including zygotes from humans, divide in vitro only to the two-cell stage, called the two-cell block, except for certain strains of mice. Only specific strains of mice can complete development in vitro from one-cell to the hollow ball stage, or blastocyst, without affecting subsequent implantation of the embryo into the uterus. Muggleton-Harris's group in the UK transferred cytoplasm from mice strains whose oocytes divide past the two-cell stage in vitro into mice whose oocytes divided only to the two-cell stage in vitro to overcome the two-cell barrier. In 1982, Muggleton-Harris, David G. Whittingham, and Lynette Wilson published their results in "Cytoplasmic Control of Preimplantation Development in vitro in the Mouse."

In 1997, Jacques Cohen, Richard Scott, Tim Schimmel, Jacob Levron, and Steen Willadsen at the Institute for Reproductive Medicine and Science of St. Barnabas in West Orange, New Jersey, announced the birth of a baby girl after the first successful human ooplasmic transfer. A patient with a history of poor embryo development in previous IVF procedures underwent ooplasmic transfer. A single sperm from the patient's husband combined with ooplasm from a twenty-seven year old donor's egg cells in a needle, and the scientists injected the sperm and ooplasm into the patient's oocytes. The researchers transferred ooplasm from seven donor egg cells into fourteen of the patient's egg cells, two for each donor egg. For a control group against which to evaluate the effects of the ooplasmic transfers, the researchers also injected only sperm into six eggs from the patient. Nine of the fourteen ooplasmic transferred eggs showed signs of fertilization, and cell division (cleavage) took place in eight of them. Researchers transferred four of those fertilized eggs through the patient's cervical opening into the uterus, resulting in a singleton pregnancy (one fetus). A girl was born at term weighing 9.6 pounds. According to Cohen and his group in their 1998 article, ooplasmic transfer restores normal growth in developmentally compromised oocytes and embryos due to advanced maternal age. They claim that ooplasmic transfer is important for older women because fertility drops off after age thirty-five in human females, and because of other IVF failures in the course of assisted reproduction.

Ooplasm contains several components, including the energy producing sub-cellular particles called

mitochondria. Mitochondria contain their own mitochondrial DNA (mtDNA) that is inherited through the egg cell's cytoplasm. When Cohen and scientists announced the birth of an infant after ooplasmic transfer in 1997, several researchers raised issues. The researchers who questioned Cohen's research included Justin C. St. John and Christopher L.R. Barratt, who worked at the University of Birmingham, Birmingham, United Kingdom, and James Cummins, who worked at Murdoch University, Murdoch, Western Australia. St. John, Barratt and Cummins questioned the method because it can add mtDNA genes to the offspring. Female offspring of ooplasmic transfer patients can transmit mtDNA from the donor to the next generation. Cohen had reported that at sixteen weeks of gestation, tests of offspring conceived with ooplasmic transfer showed that maternal mtDNA had displaced donor mtDNA. But his critics argued that gave no indication of the accuracy of this result. If the donor's mtDNA survived, the offspring would be the recipient of parts of the genome from the mother and father, and mtDNA from the ooplasm donor. Illnesses can occur when there is a mixture of mtDNA in mitochondria, called heteroplasmy, as it can lead to several mitochondrial diseases that affect muscles, the brain, and the endocrine system.

When Cohen's group released their findings in 1997, the press hailed the result as a technological breakthrough. On 5 May 2001, the Daily Mail reported that thirty babies were born using ooplasmic transfer. Fifteen were born at Cohen's New Jersey's Institute for Reproductive Medicine and Science of St. Barnabas, stating that the oldest turned four in June 2001. Two babies were born after 2001. The institute was among the first to use the technique, and another fifteen babies were born using this technique at other institutions over the course of four years after 1997. Two of the infants from the St. Barnabas Clinic had a mixture of maternal mtDNA and donor mtDNA. In 2001, Cohen said these children were doing well. Shannon Brownlee in 2002 reported that doctors diagnosed one of the children conceived through ooplasmic transfer with pervasive developmental disorder, a general diagnosis that can indicate mild developmental delays to severe autism. Cohen's group maintained that it was unlikely that mismatch of mtDNA was to blame.

In 1998 the US Food and Drug Administration (FDA) banned the procedure. The FDA argued that genetically manipulated embryos are a biological product and therefore subject to FDA regulations, like medical devices and drugs. In 2001, after the FDA sent warning letters to six fertility clinics threatening legal action, Cohen's St. Barnabas clinic stopped performing ooplasmic transfers. Other clinics challenged the FDA's authority and continued performing ooplasmic transfers. In February of 2014, the FDA held public meetings to discuss mitochondrial manipulation techniques. There was no formal decision made on the efficacy of the treatment, but the committee agreed that with more experimentation on animal models to provide further scientific data, potential benefits of ooplasmic transfer could outweigh concerns.

Sources

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