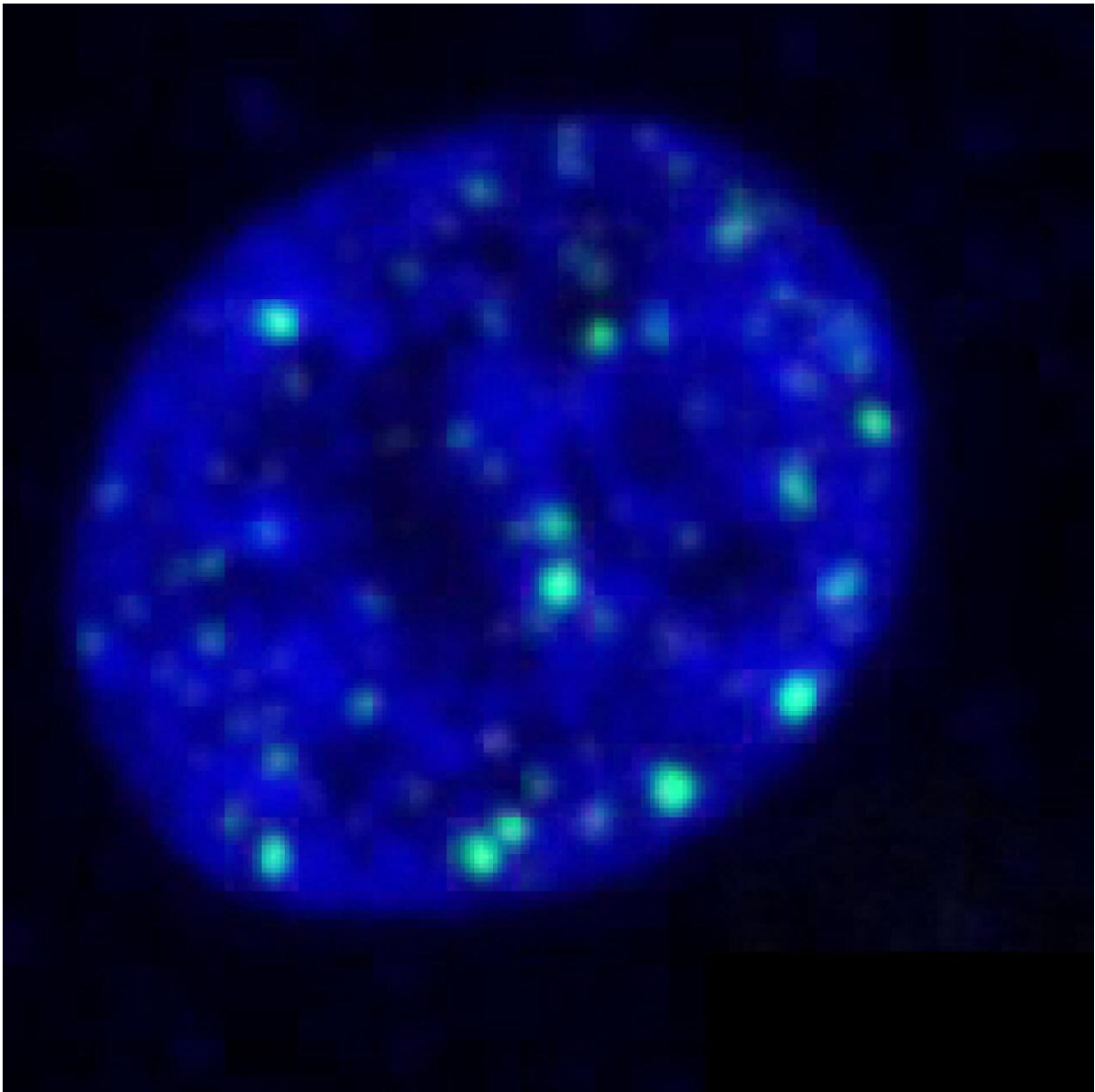


# Study finds why many IVF embryos fail to develop

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Day 3 human embryo with DNA breakage (green) in the DNA (blue). Credit: Egli lab, Columbia University Irving Medical Center

In humans, a fertilized egg is no guarantee of reproductive success. Most embryos stop developing and perish within days of fertilization, usually because they have an abnormal number of chromosomes. Now, researchers at Columbia University Vagelos College of Physicians and Surgeons have found that most of these mistakes are due to spontaneous errors in DNA replication in the earliest phase of cell division.

The findings provide new insights into the basic biology of human reproduction and in the long term could lead to improvements in the success rate of in vitro fertilization (IVF). The study was published online July 19 in the journal *Cell*.

## **Challenging task for early embryos**

Approximately 24 hours after a human egg is fertilized, the process of [cell division](#) begins. During cell division, the [entire genome](#)—46 chromosomes containing more than 3 billion base pairs of DNA—must be faithfully duplicated. The duplicate sets of chromosomes must then be separated so that each daughter cell receives a complete set.

In many [human embryos](#) created for IVF, something goes wrong and some cells within the embryo have too few or too many chromosomes.

"Duplicating the genome is a challenging task for the early embryo," says study leader Dieter Egli, Ph.D., the Maimonides Assistant Professor of Developmental Cell Biology (in pediatrics) at Columbia University Vagelos College of Physicians and Surgeons.

Researchers have long theorized that errors occur during the final phase of cell division, when the duplicate sets of chromosomes separate into two identical daughter cells. Most of these failures were attributed to issues with the microtubule spindle, the apparatus that pulls the two sets of chromosomes apart.

But Egli's studies found that chromosomal abnormalities stem from errors that occur much earlier in the process of cell division when the genome's DNA is duplicated. If the DNA is not copied precisely, his studies found, the spindle malfunctions and places the wrong number of chromosomes into each daughter cell. When DNA duplication is abnormal, the spindle does not function normally. "This has largely been overlooked in previous studies—because why would the embryo allow the integrity of the genome to be compromised when this is such a critical requirement for [normal development](#)?" Egli says.

Though the studies were conducted with embryos created in a [petri dish](#)—including from individuals undergoing IVF and egg donors who were not seeking fertility treatment—the same problems may contribute to the failure of embryos created in natural human reproduction.

## **Clues to source of DNA errors**

The source of DNA copying errors in embryos appears to spring from obstacles within the DNA's double helix. Though the precise reason for these obstacles is not yet known, they cause duplication of the DNA to pause, or even stop, which results in DNA breakage and an abnormal number of chromosomes.

Spontaneous DNA errors can occur as early as the first cycle of cell division in human embryos, the researchers found, as well as in subsequent cell divisions. If too many cells in the early embryo are affected by [chromosomal abnormalities](#), the embryo cannot develop

further.

## IVF

Most human [embryos](#) created for IVF stop developing within days after fertilization. This inefficiency of human development is an obstacle to successful fertility treatments.

"Many women undergoing [fertility treatment](#) require multiple IVF cycles in order to get pregnant, and some never get pregnant at all. Not only is this enormously expensive, it's emotionally taxing," says Jenna Turocy, MD, a fertility specialist at Columbia University Fertility Center and a co-author of the study.

The researchers are planning additional studies looking at DNA damage during replication in the hope of understanding normal and disease-causing variations in the [human](#) germ line. In the long term, these studies may lead to methods to reduce the risk of genetic abnormalities and embryo attrition for patients undergoing IVF.

**More information:** Katherine L. Palmerola et al, Replication stress impairs chromosome segregation and preimplantation development in human embryos, *Cell* (2022). [DOI: 10.1016/j.cell.2022.06.028](https://doi.org/10.1016/j.cell.2022.06.028)

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