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Gene therapy that uses 3 parents holds promise

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Scientists revisit fertilization technique to address birth defects

BY KAREN WEINTRAUB

Alana Saarinen sat at the piano, playing smoothly and with feeling. Behind her, plastic toys shared floor space with a book of plays she'd been writing. Her mother beamed.

Alana is apparently a normal, well-adjusted 13-year-old. But there is something extraordinary about her — every cell in her body is different in a way that is nearly unprecedented.

Alana was conceived with genetic material from three parents: Sharon and Paul Saarinen, who provided the egg and sperm, and a second woman who contributed genes to Alana's mitochondria, the tiny power plants that fuel every cell.

The experimental technique making this possible — a cytoplasmic transfer, in Alana's case — was halted by the Food and Drug Administration in 2001. Now, despite uncertainties about its safety, scientists in the United States and the United Kingdom are urging legalization of a more targeted version. Critics say it hasn't been adequately studied and crosses the line into genetic engineering.

Mitochondria are minute organelles inside living cells, floating apart from the nucleus in the cytoplasm. They create energy for the cell's activities. While most of the cell's DNA lies in the nucleus, each mitochondrion contains its own small set of 37 genes, inherited solely from mothers. The genes governing production of mitochondria, both in the nucleus and in the organelle itself, can be defective, and the defects can be passed from mothers to their children. Mitochondrial diseases are rare, but they can be devastating and are incurable.

Scientists have been testing fertilization techniques that would permit a woman with mitochondrial defects to have children who are genetically her own without passing on abnormalities.

Researchers who want the techniques approved say there's no evidence of harm and a clear benefit to a number of women who could not have healthy children any other way. "This to me seems to clearly fall on the side of ethical and permissible," said Nita Farahany, a professor of law, philosophy and genome sciences and policy at Duke University. The technique is "not only promising, but morally preferable to leaving a woman without a choice for having her own healthy genetic children."

Other experts argue that the science is far too experimental to be used for a pregnancy, especially when a woman could opt for a donor egg or adopt.

"What negative, debilitating implications are we offering into the germline? What are we saddling future generations with?" said Jeremy Gruber, president of the Council for Responsible Genetics, a New York-based advocacy group.

The technique has an unusual history. In the late 1990s, Dr. Jacques Cohen, a fertility specialist then at Saint Barnabas Medical Center in Livingston, N.J., believed that by inserting cytoplasmic material, including mitochondria, from a healthy egg cell into an infertile patient's egg cell, he significantly increased the chances it would thrive. He was careful not to transfer the nucleus of the donor egg, seat of the genome.

Dr. Cohen's work led to the birth of 17 babies, all initially healthy. One pregnancy that was begun with a cytoplasm transfer ended in miscarriage, however, while another was aborted. In both instances, the fetus would have had Turner syndrome, a genetic abnormality of the sex chromosome.

Moreover, the cells of at least two children held a mix of mitochondria from both their mothers and from donor women. Studies of mice have suggested that this may lead to mental impairment and a greater risk of obesity and disease.

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Other fertility clinics tried Dr. Cohen's procedure, which likely led to about 100 births worldwide, including Alana Saarinen's. In 2001, the F.D.A. warned the facilities to obtain formal approval or stop the procedure. All of them stopped.

But newer mitochondrial replacement techniques may be safer than the pioneering work done years ago, proponents say, because nearly all of the mitochondria in the fertilized egg cell are replaced by the donor's. Rhesus-monkeys born with replacement mitochondria appear normal, according to research by Shoukhrat Mitalipov, a reproductive-biology specialist at Oregon Health and Science University.

Dr. Mitalipov has asked the F.D.A. for permission to conduct clinical trials in humans. Approval seems more likely in the United Kingdom, where scientists have been lobbying for years for mitochondrial transplants. Parliament is expected to vote on legalization of the technique in about a year.

Mrs. Saarinen, a hairdresser in suburban Detroit, believes the case for a new kind of fertility treatment is already clear. Her daughter Alana — athletic, smart and slim — has never been sick with anything worse than the flu. "I've got the living proof every day," she said.