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Technology Quarterly | Reproductive science

Designing babies

Will tinkering with human embryos ever be worth the risk?

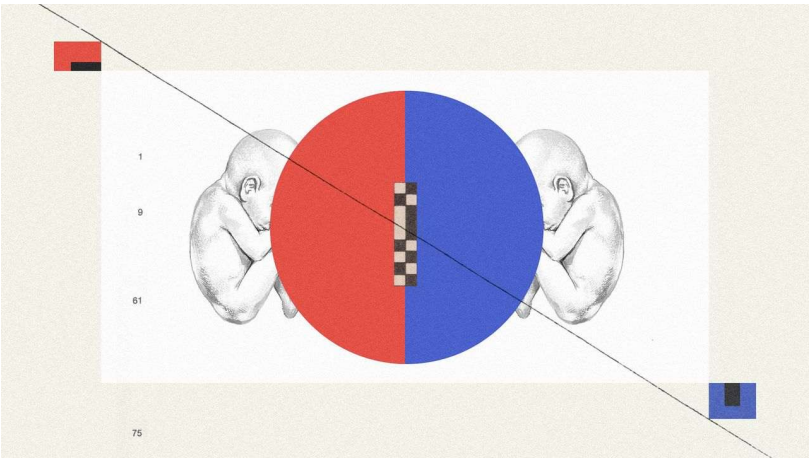

Illustration: Mark Weaver

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One of the greatest scandals in modern science began with a late-2010s advertisement for HIV-positive couples looking to have children through *in-vitro* fertilisation (IVF). The ad had been put out by a scientist named He Jiankui, a biologist then at the Southern University of Science and Technology in China. Several pairs responded. For each couple, Dr He and his team harvested their sperm and eggs and created embryos through IVF. He edited a gene in each embryo using CRISPR, then did something that had never been done before: had the edited embryos implanted into the women's wombs.

The gene, CCR5, is responsible for a cell-surface protein which plays a key role in HIV infection. A natural variant of CCR5 blocks production of the protein and confers protection against HIV. It was this protection that Dr He sought to give the embryos. In November 2018, just before the second International Summit on Human Genome Editing, *MIT Technology Review* reported both that the experiments had taken place and that two of the embryos had, when implanted in the womb, resulted in successful births. As a result there were now two little girls with edited genomes.

Science friction

At the summit, Dr He appeared unprepared for the uproar that followed. His colleagues, who considered such experimentation premature and unsafe, were outraged. Slowly it became clear that not only did Dr He's work have technical failings, but also he had broken the rules within which scientists must operate. The informed consent of the parents seemed questionable; according to Chinese news reports, he had forged approval documents from an ethics review board. On top of all that, China forbids gene editing in human reproduction, and Dr He was not licensed to practice medicine. Dr He was detained by Chinese authorities and eventually sentenced to three years in prison for the illegal practice of medicine.

The condemnation of Dr He's work reflected in part a judgment of his careless approach to the lives of the people he "treated". The world knows nothing about the twins and the state of their health, nor about a possible third CRISPR child which was reported to have been born to another couple shortly after the twins. Questions about the quality of the edits themselves and what repercussions they might have on the children thus remain unanswered.

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But underneath the outrage lay long-running concerns about the fundamental concept of editing embryos. Edits which take place that early in the developmental process are passed on to every other cell as the embryo grows,

including the “germline” cells that will eventually produce sperm or eggs. If nothing is done later to reverse them, they will thus be passed on down the generations—unlike the sort of CRISPR edit that cures a disease in someone already born. By definition future generations cannot give their informed consent to a procedure that takes place long before they are conceived. For that reason embryo editing is in effect banned in many European countries under the Oviedo Convention. (Many other countries, including Britain and Canada, also legally forbid the practice.)

The main attraction of embryo editing is that it allows edits which are very difficult or impossible later on. When editing a person who has already been born, some tissues, such as the brain, are very hard to reach. Embryo editing does not have that problem, as all the cells that go on to form the organs will in theory carry the edit. There are also people who think passing on an edit is not such a bad thing. Families in which successive generations have battled the same genetic disease often wish to spare their descendants the same fate, says Dagan Wells, a reproductive biologist at the University of Oxford (he is agnostic on the procedure).

Tailored genes

In January 2025 a paper appeared in *Nature* discussing the societal benefit of polygenic embryo editing—that is, making several edits in the same embryo. Rather than just curing genetic diseases, it could tweak multiple genes that together alter the risk of conditions like Alzheimer’s disease or diabetes. The authors, led by Julian Savulescu, an Australian philosopher, acknowledged that the concept is speculative but suggested that it could dramatically benefit those who are edited. But what about those who are not edited?

The question of precisely who gets edited, and for what purpose, cuts to the heart of concerns around germline editing. Families struck by a genetic disease probably would benefit but they are in relative terms a fairly small group. Many will be interested in enhancements that polygenic embryo editing could offer. At first that might mean adding protection for preventable disease. But eventually it could mean tweaking traits like appearance and intelligence—in other words, creating designer babies. Some worry the rich would edit their offspring “better” and that people with disabilities or who are simply average would be put at greater disadvantage. “Gene-editing techniques applied to non-disease traits may deepen inequalities and raise the spectre of eugenics,” argued Dr Savulescu and his team in their paper.

Others think it is far from clear that edited people will indeed benefit. A genetic variant that is advantageous in one context may be bad in another. The variant of CCR5 that protects against HIV, for example, has been linked to an increased risk of complications and even death during other infections. These unknowns are worth worrying about, argues Hank Greely, a lawyer at Stanford University and the author of the book “CRISPR People: The Science and Ethics of Editing Humans”. His main objection to Dr He’s CCR5 project was that its risk-benefit ratio was unacceptable: the benefits, if there were any, would be limited, and the risks, both any which were known and those yet to be understood, were potentially substantial. Dr He, who is out of prison and apparently back in a laboratory—the sources of his funding as yet unclear—is unfazed by this ignorance. His new germline project focuses on a rare variant found in Icelanders which protects against Alzheimer’s, though he has promised not to create any more pregnancies.

There are also signs that editing embryos might in itself be unsafe. Like regular gene editing, germline editing depends on natural repair mechanisms stepping in after an editor has made its cut. But when Dr Wells and Nada Kubikova, another Oxford scientist, used CRISPR to make 53 double-stranded breaks in human embryos, 21 of them remained unfixed (the embryos had been donated to science and were never going to be implanted). Dr Wells reckons the problem stems from the biology of the early embryo. For the first two to three days, the embryo mostly relies on proteins and mRNA from the egg instead of its own genome. During that time it struggles to repair injuries to its DNA, and any cuts left as the embryo develops could prove deleterious. With such bad odds, couples would need many embryos to ensure success.

Fetal attraction

With so many outstanding concerns, Dr Greely does not see germline editing taking off in the next few decades. But a less ethically fraught option may be on the way. Several groups are working on *in utero* genome editing. Done late enough in development it would not alter germline cells, but would still give doctors a chance to

repair a genetic mutation before the baby is born. Like embryo editing it might be able to reach otherwise hard-to-access cells.

Early results have been encouraging. At the Children's Hospital of Philadelphia, William Peranteau has averted disease in mice using fetal editing, and successfully edited fetal monkeys. A group led by Panicos Shangaris at King's College London is working specifically on fixing the sickle-cell mutation this way. In sickle-cell disease scientists must fix the stem cells that go on to make blood. During the fetal stage of development these all reside in the liver, which is easy to reach with an injection into the umbilical cord. The approach could be especially useful for when the pathology starts early. Lysosomal storage diseases, in which cells fail to break down waste properly, begin in the womb. "You miss your window treating it if you wait till after birth," says Dr Peranteau. It might even be possible for fetal edits to reach the brain.

All conditions that become more difficult to treat after birth could be candidates for such editing. Epidermolysis bullosa is a terrible blistering disease that affects all skin and the oesophagus. Researchers led by Joanna Jackow at King's College London are working on developing a "gene cream" that fixes the genetic mutation directly in the skin's stem cells, but administering it is a massive challenge because children with the condition are covered in open wounds. Fetal editing might be able to reach those cells more easily.

The lure of germline editing, though, is unlikely to go away. Dr He's return to the lab suggests that the scientific establishment's condemnation was not as powerful as it first appeared. Rogues like him could well find patrons among the super wealthy. Billionaires with interests in reproductive technology and human enhancement—of whom there are several—might see both personal and business opportunities in embryo editing. People opposed to abortion might see germline editing as a way to avoid discarding or terminating embryos; Dr He has himself referred to editing an embryo as "saving a life". (Conversely, fundamentalist Christians may find the idea of editing embryos to be sacrilegious.) Whether CRISPR babies become a near-future reality may depend on whether such powerful interests become invested in the prospect. ■