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Making babies: How to create human embryos with no egg or sperm

Artificial wombs and embryos made from skin cells – remarkable new techniques could revolutionise reproductive biology and help bring an end to infertility

Neil Bromhall/Science Photo Library

By **Elie Dolgin**

YUE SHAO wasn't trying to create an embryo. But, a few years ago, working in a lab at the University of Michigan, he witnessed something mind-boggling. The cells he was working with seemed to assemble themselves into what looked just like an early-stage human.

"We were looking for something else," says Shao, a bioengineer now at the Massachusetts Institute of Technology – but "serendipity hit".

The idea that scientists could create the first steps towards human life is astonishing, but Shao's discovery wasn't the first. A year before he published his results in 2017, research by a team in Japan led to the birth of live mouse pups using eggs the team made from adult skin cells.

Discoveries like these are bringing us closer to solving some of the most intractable problems in reproductive biology and medicine. By recreating these first days of development in the lab, researchers are breaking open the black box of early pregnancy, a poorly understood and fragile time at which most miscarriages happen and fertility treatments fail.

Now 40 years after the birth of the first test-tube baby, the potential of these breakthroughs is heralding a new biological revolution, one that forces us to rethink what it means to reproduce and make a baby. And there's a lot to consider. Imagine being able to conceive a child from someone's skin cells, for instance – with or without their consent. Given the ability to make a human artificially, we need to decide whether we want to.

Already, some 1.5 per cent of all babies born in western Europe, North America and Australia are conceived using in vitro fertilisation (IVF). So making the spark of life outside the body is routine. But it is also unpredictable. So much is still unknown about why some embryos don't implant after transfer or, in both IVF and natural conceptions, what causes some to die while others keep growing. IVF also relies on prospective parents having viable sperm and eggs to work with in the first place.

Perhaps the boldest attempt so far at getting around that problem is to make sperm and eggs from totally unrelated cells in the body. Working with mice, Mitinori Saitou of Kyoto University in Japan and his collaborators took adult skin cells and reprogrammed them into stem cells, which have the potential to become any type of cell. They then turned these into either sperm or eggs. In 2016, they reported that they had fertilised some of these eggs with sperm from normal mice, and implanted the embryos into surrogates. Eight seemingly healthy pups were born. Then a year later, working with a team from the Crick Institute in London, they did the corresponding experiment using their lab-made sperm.

"It could lead to less invasive IVF or help women who are being treated for cancer"

The potential for treating infertility is huge (see "Why make babies from skin cells?") but attempts at creating human sperm and eggs in the lab have so far produced only rudimentary precursors to these sex cells. For example, Azim Surani, a developmental biologist at the University of Cambridge's Gurdon Institute, announced in late 2017 that his team had managed to grow "primordial germ cells" – precursors of sperm and eggs – to the four-week mark. Next, he hopes to nurture these cells to eight weeks, the point at which they either go on to form sperm or eggs.

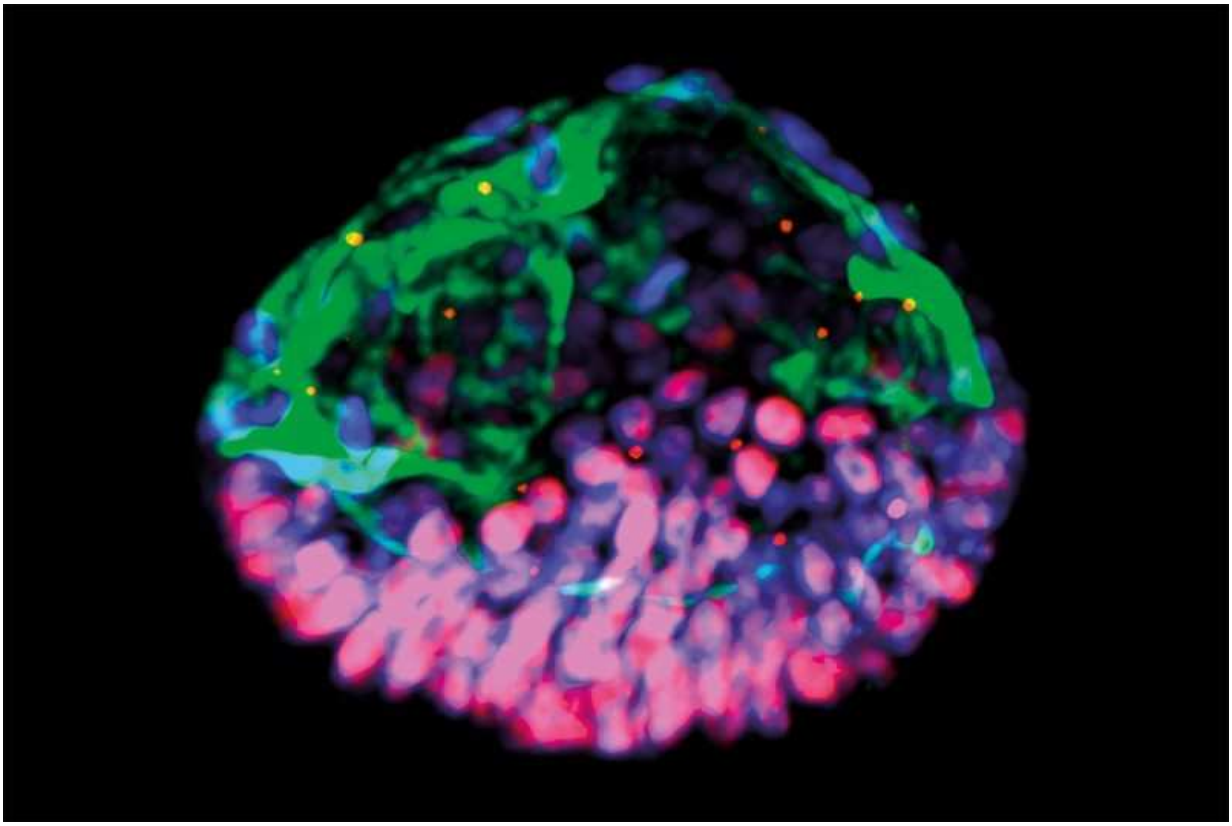
It is possible that if these were transplanted into the body, they would mature and restore fertility in otherwise infertile individuals, says Werner Neuhausser, a stem-cell biologist at Harvard University. But, he adds, "there's a whole other layer of safety issues that will have to be dealt with before this would ever enter clinical practice".

And we are still a long way from finishing the process in a lab dish.

One promising advance came earlier this year, when Evelyn Telfer at the University of Edinburgh, UK, and her colleagues cultured mature human eggs in the lab from a different type of stem cell found in ovaries. Telfer envisions using this technique to help women with cancer, where treatment can cause infertility. The idea would be to remove a piece of the ovaries before treatment, and to use it later on to make new eggs. It could also lead to "next-generation IVF", Telfer says, in which women would undergo a one-off surgical procedure to retrieve ovarian tissue, instead of successive cycles of hormones and invasive egg-harvesting.

Alternatively, we might not need to make eggs or sperm at all. Last year, a team led by Magdalena Zernicka-Goetz at the University of Cambridge coaxed two different kinds of mouse stem cells to assemble into a structure that, after three or four days in a lab dish, looked and behaved the same way as a natural embryo. "Superficially, they were very, very similar," says Sarah Harrison, who worked on the project as a PhD student.

Five months later, Shao's group published its creation of comparable "embryoids" made entirely with human stem cells (see image, below).



A five-day-old human embryoid, created from stem cells with no sperm or egg
Yue Shao, University Of Michigan

In both cases, the impetus for the research was a desire to understand the early stages of embryo formation, which are difficult to study inside the body – specifically, what happens after an embryo implants in the uterus and starts organising its cells into layers. Shao also envisions his embryoids providing a platform for screening drugs and environmental toxins to see whether they cause birth defects. Neither team is trying to make viable embryos.

Besides, after four or five days these embryo-like structures already look more like two-week-old natural human embryos. That means they have effectively skipped the earliest steps of development and missed the stage at which implantation is feasible.

So the only shot at viability that these lab-grown embryoids might have would be outside the womb. Until recently, that prospect would have been unimaginable, because no one had succeeded in nurturing human embryos in a dish past the implantation stage. But two years ago, separate teams led by Zernicka-Goetz and Ali Brivanlou, an embryologist at Rockefeller University in New York, described ways of getting human embryos to develop for up to two weeks after fertilisation. And they might have gone even longer were it not for the "14-day rule", a legal and regulatory line in the sand agreed by most countries engaged in research on human embryos.

That cut-off was chosen because it is the time at which a faint band of cells known as the primitive streak appears, a key developmental milestone for complex tissue formation. It is also when an embryo can no longer split into identical twins, and so it has been defined by some as the moment a distinct biological entity comes into being.

With that definition in mind, many scientists are now scrambling to figure out how best to apply the 14-day rule to research on embryoids like the kind Shao's team created – or even whether the rule applies at all. Last year, a team led by John Aach and George Church, geneticists at Harvard Medical School, gave these structures a name –synthetic human entities with embryo-like features, or SHEEFs – and called for a broad international discussion of ethical issues raised by their creation.

As bioethicist Sarah Chan at the University of Edinburgh points out, a mass of self-assembling stem cells doesn't have a clear day zero from which to start counting, so 14 days is meaningless. What's more, because SHEEFs don't develop along the conventional pathway, they may acquire morally concerning features long before the primitive streak is visible at 14 days. "We need to have this wide-ranging debate," Chan says.

As developments like these push how long we can grow embryoids in the lab, others are working away at one of the most daunting challenges in reproductive medicine – how to keep babies alive when they enter the world too early. According to David Adamson, a reproductive endocrinologist who runs Advanced Reproductive Care, a US-wide network of fertility clinics, this "will be exceptionally difficult, and not achievable in this century".

There are good reasons to try, though. Neonatologists are advised against trying to save the lives of babies born before 22 weeks because of limitations with existing resuscitation technologies. An artificial womb could change that.

Last year, fetal surgeon Alan Flake and his colleagues at Children's Hospital of Philadelphia described one such invention: a fluid-filled sac dubbed the Biobag. It kept lambs alive for about four weeks after they had been born at the equivalent of about 23 to 24 weeks in a human pregnancy, judged by lung development. Survival for premature babies is currently less than 50 per cent at that stage.

For the lambs, this and other systems, like the "artificial placenta" developed by George Mychaliska's team at the University of Michigan's Extracorporeal Life Research Laboratory, can serve as a bridge until the lambs are ready for artificial ventilators and eventually to transition to breathing on their own.

The next generation

"It does appear that the lungs are continuing to develop over time, and they're

protected," Mychaliska says. In March, his team showed that the lambs' brains develop normally, too. "The goal is clinical translation in five years," he says. Human trials will initially include premature babies who have less than a 20 per cent chance of survival.

If one of these womb-like systems works for humans, it opens the door not just to sparking life in the lab, but keeping it alive entirely outside of the body. All these baby steps in our quest to improve the human condition could thus add up to the giant leap of making life from scratch. "My guess is this would be a major way of having babies 100 years from now," says Hank Greely, a bioethicist and lawyer at Stanford University in California. "Once you get 50 or 60 years out, the sky is the limit with biology."

Others are less bullish. "A lot of things have to go very, very wrong – and have been very wrong for a while – before that would seem like a good idea," says Gigi Gronvall at the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland.

And Jeantine Lunshof, a bioethicist at the University Medical Center Groningen in the Netherlands, says: "Given the ease of making babies, in general, I do not see any need for it, nor arguments to support such an endeavour."

Louise Brown was the first child to be conceived using in vitro fertilisation, in 1978
Michel Artault/Gamma-Rapho/Getty Images

Yet similar things were once said about IVF: it was too dangerous, an unnatural and immoral abomination. Then came the birth of the first "test-tube baby" Louise Brown in 1978. An estimated 7 million have followed since. Now the fertility technique is practically routine, and few outside certain religious circles continue to debate its merit.

A similar acceptance could prevail for the next generation of assisted-reproductive treatments.

One reason to continue towards the goal of a complete from-scratch baby would be

protection against some kind of environmental catastrophe or nuclear disaster. Think *Children of Men* or *The Handmaid's Tale*. "If the human race as a whole were seriously endangered, and if our reproductive abilities were seriously compromised, we might have to manufacture human beings," says Ronald Green, a retired ethicist from Dartmouth College in Hanover, New Hampshire.

More likely, says Anna Smajdor, a bioethicist and philosopher at the University of Oslo, Norway, the ability to build human life from scratch would occur more as an after-effect than as a deliberate goal of reproductive research. As new technologies develop for bona fide medical reasons – treating infertility, preventing the transmission of genetic disease, saving the lives of premature babies – "you'll get this creep," she says.

Whatever the driver, it is undeniable that a huge biological shift is under way. Still, if experiments like Shao's tell us anything, it's that whether you are doing it in the lab or the old fashioned way, when it comes to the spark of life, you can never predict the outcome.

Why make babies from skin cells?

Once it becomes possible to grow sperm and eggs in the lab from anybody's skin cells (see main story), people in wealthier countries with robust healthcare systems may even stop having sex for baby-making purposes, says Hank Greely at Stanford Law School in California.

"As people see that kids born this way don't have three heads and a tail, and as they begin to notice family members and friends who've had a kid with a serious disease that could be prevented," he says, "people will put themselves out for their children's health."

Greely envisions a future in which prospective parents would make an appointment at their local fertility clinic. A small sample of skin cells would be used to make stem cells from which sperm and eggs would be derived, before creating dozens, if not hundreds or even thousands of thriving embryos. After genetic screening, parents could pick the one they want to transfer.

It would put an end to the painful, invasive and expensive process of egg-retrieval during IVF. And those people incapable of making their own sperm or eggs could have genetically related children. So could same-sex couples.

But such technology also raises serious ethical questions. Although screening could rule out devastating genetic diseases, it would open the door to routine sex selection and other choices for non-medical reasons. And while it is already possible to access to this kind of information, its application is limited. Our rudimentary knowledge about how small genetic differences add up to something like IQ restricts things, as does the fact that egg-harvesting yields a maximum of a few dozen eggs per cycle.

"It's going to be very difficult to restrict that kind of information, and it might even seem perverse to try," says Anna Smajdor, a bioethicist and philosopher at the University of Oslo in Norway.

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Elie Dolgin is a science writer in Somerville, Massachusetts

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