Why it is so hard for humans to have a baby?

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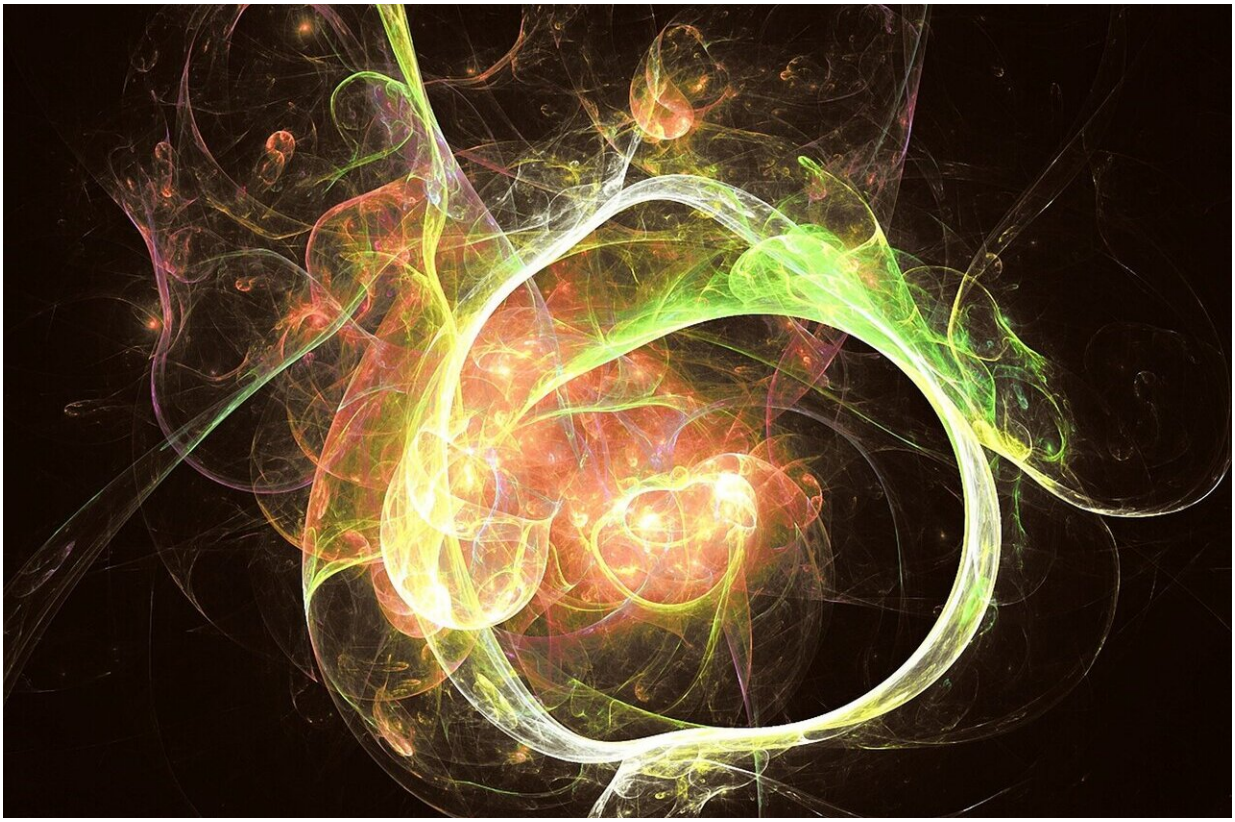

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New research by a scientist at the Milner Center for Evolution at the University of Bath suggests that "selfish chromosomes" explain why most human embryos die very early on. The study, published in *PLoS Biology*, explaining why fish embryos are fine but sadly humans' embryos often don't survive, has implications for the treatment of

infertility.

About half of fertilized eggs die very early on, before a mother even knows she is pregnant. Tragically, many of those that survive to become a recognized pregnancy will be spontaneously aborted after a few weeks. Such miscarriages are both remarkably common and highly distressing.

Professor Laurence Hurst, Director of the Milner Center for Evolution, investigated why, despite hundreds of thousands of years of evolution, it's still so comparatively hard for humans to have a baby.

The immediate cause of much of these early deaths is that the embryos have the wrong number of chromosomes. Fertilized eggs should have 46 chromosomes, 23 from mum in the eggs, 23 from dad in the sperm.

Professor Hurst said: "Very many embryos have the wrong number of chromosomes, often 45 or 47, and nearly all of these die in the womb. Even in cases like Down syndrome with three copies of chromosome 21, about 80% sadly will not make it to term."

Why then should gain or loss of one chromosome be so very common when it is also so lethal?

There are number of clues that Hurst put together. Firstly, when the embryo has the wrong number of chromosomes it is usually due to mistakes that occur when the eggs are made in the mother, not when the sperm is made in the father. In fact, over 70% of eggs made have the wrong number of chromosomes.

Secondly, the mistakes happen in the first of two steps in the manufacture of eggs. This first step, it had been noticed before, is vulnerable to mutations that interfere with the process, such that the mutation can "selfishly" sneak into more than 50% of the eggs, forcing

the partner chromosome to be destroyed, a process known as centromeric drive. This is well studied in mice, long suspected in humans and previously suggested to somehow relate to the problem of chromosome loss or gain.

What Hurst noticed was that, in mammals, a selfish mutation that tries to do this but fails, resulting in an egg with one too many or one too few chromosomes, can still be evolutionarily better off. In mammals, because the mother continuously feeds the developing fetus in the womb, it is evolutionarily beneficial for embryos developing from faulty eggs to be lost earlier rather than be carried to full term. This means that the surviving offspring do better than the average.

Hurst explained: "This first step of making eggs is odd. One chromosome of a pair will go to the egg the other will be destroyed. But if a chromosome 'knows' it is going to be destroyed it has nothing to lose, so to speak. Remarkable recent molecular evidence has found that when some chromosomes detect that they are about to be destroyed during this first step, they change what they do to prevent being destroyed, potentially causing chromosome loss or gain, and the death of the embryo.

"What is remarkable, is that if the death of the embryo benefits the other offspring of that mother, as the selfish chromosome will often be in the brothers and sisters that get the extra food, the mutation is better off because it kills embryos".

"Fish and amphibians don't have this problem", Hurst commented. "In over 2000 fish embryos not one was found with chromosomal errors from mum". Rates in birds are also very low, about 1/25th the rate in mammals. This, Hurst notes, is as predicted as there is some competition between nestlings after they hatch, but not before.

By contrast, chromosome loss or gain is a problem for every mammal that has been looked at. Hurst commented, "It is a downside of feeding our offspring in the womb. If they die early on, the survivors benefit. It leaves us vulnerable to this sort of mutation."

Hurst suspects that humans may indeed be especially vulnerable. In mice the death of an embryo gives resources to the survivors in the same brood. This is gives about a 10% increase in survival chance of the others. Humans, however, usually just have one baby at a time and the death of an embryo early on enables a mother to rapidly reproduce again—she probably never even knew her egg had been fertilized.

Preliminary data shows mammals such as cows, with one embryo at a time seem to have especially high embryo death rates owing to chromosomal errors, while those with many embryos in a brood, like mice and pigs, seem to have somewhat lower rates.

Hurst's research also suggests that low levels of a protein called Bub1 could cause loss or gain of a chromosome in humans as well as mice.

Hurst said: "The levels of Bub1 go down as mothers get older and as the rate of embryonic chromosomal problems goes up. Identifying these suppressor proteins and increasing their level in older mothers could restore fertility.

"I would hope too that these insights will be one step to helping those women who experience difficulties getting pregnant, or suffer recurrent miscarriage."

More information: Selfish centromeres and the wastefulness of human reproduction, *PLoS Biology* (2022). DOI: 10.1371/journal.pbio.3001671

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