The next debate on embryo science

The International Society for Stem Cell Research has called for broad public dialogue on the ethics of human embryo research beyond 14 days post-fertilization. National jurisdictions should seize the moment.

A longstanding prohibition against culturing human embryos for more than 14 days is now open for discussion, according to revised research [guidelines](#) released in May by the International Society for Stem Cell Research (ISSCR). The society's change in position was prompted by recent advances in embryo culture methods that promise to deepen understanding of human development at the stage when the embryo implants in the uterus—knowledge that may lead to new therapies for infertility and miscarriage. The ISSCR is to be commended for encouraging ethical reflection on extending the 14-day rule before the world is caught off guard by an embryo experiment that goes beyond the accepted time frame. It is now up to interested parties in national scientific, political, ethics and religious communities to take up the ISSCR's challenge.

In 1978, the birth of the first baby created through in vitro fertilization (IVF) was met with a storm of controversy. IVF provoked deep concerns and anxieties about the wisdom of tampering with the natural order of reproduction. Once human procreation was unlinked from coitus, impossible things became possible: women bearing genetically unrelated children, postmenopausal women giving birth, embryos selected in a lab. The public and scientists alike wanted safeguards that placed limits on the new technology.

A 14-day limit on embryo research was proposed the following year and subsequently considered by a UK committee convened to advise on the regulation of human assisted reproduction. In its 1984 [report](#), the committee, chaired by Mary Warnock, enshrined the 14-day limit among its 64 recommendations. But the question of how long IVF embryos could be kept in culture was especially contested, and various developmental milestones were contemplated, including the end of the implantation period (day 13); the beginning of the implantation period (day 6); the formation of the primitive streak, when individuation occurs (day 15); early neural development (day 17); and the emergence

of the central nervous system (days 22–23). Fourteen days represented a compromise.

In the decades since the Warnock report, the 14-day rule has been adopted around the world, although national implementations have varied and regulations in some countries are more strict. Likewise, the ISSCR has long incorporated the rule in its guidelines for stem-cell scientists. In its updated guidelines, the ISSCR now says that culture of human embryos beyond 14 days is no longer strictly forbidden and may be permitted by local jurisdictions conditional on thorough societal, ethics and scientific oversight. Public oversight is the crucial prerequisite. “[T]he ISSCR calls for national academies of science, academic societies, funders, and regulators to lead public conversations touching on the scientific significance as well as the societal and ethical issues raised by allowing such research [involving culture beyond 14 days].”

The ISSCR guidelines do not jettison the Warnock rule. But it's time, they say, to talk about it.

The change was motivated by advances in embryo science. Human embryos cannot be kept alive in vitro for very long, but with recent improved [methods](#), robust cultures to 14 days and beyond are now within reach. Extending culture through the implantation and early post-implantation stages is technically difficult because this would mean mimicking the uterus, or uterine function, in a dish. Achieving this goal would open new avenues for understanding human reproduction and development, and how these go wrong in infertility and miscarriage.

It would also benefit the emerging field of stem cell–derived embryo models that mimic specific parts of development, like the gastrulation stage (‘gastruloids’) or the blastocyst stage (‘blastoids’), rather than a whole embryo. Eventually, these models could reduce the use of embryos in research. But first, to assess their quality and utility, scientists would have to compare them side by side with real embryos grown to the equivalent stage.

The ISSCR has put the world on notice. Embryo culture methods are advancing steadily, along with work in related areas like germline genome editing and stem cell–derived gametes, and societies need to get ahead of the science by following research developments and grappling with their ethical and regulatory implications. Any such debates that included a diversity of cultural and religious perspectives are sure to be contentious. Even the ISSCR could not agree on a new line to replace the 14-day rule. “In the end, the reason we did not come up with a specific guideline is that we could not come to any kind of reasonable consensus on what that guideline would be,” said Janet Rossant, a member of the task force's steering committee.

It remains to be seen whether the question of extending the 14-day rule will ignite wide interest. The public is attuned to certain issues concerning human embryo research, like IVF, [human embryonic stem cells](#) and, most recently, germline genome editing. In those instances, both the technology's perils and its potential to promote human well-being capture the public imagination. In contrast, the ethical intricacies and uncertain health benefits of relaxing the 14-day rule do not make for flashy headlines, so it is hard to see this issue being prioritized. Broad societal discussions may await a research breakthrough that places embryo culture back in the public eye.

Targeted germline editing became a realistic possibility in the 1990s with the development of engineered zinc finger nucleases. But it was only the shock of He Jiankui's 2018 announcement of the birth of genome-edited babies that galvanized oversight by authorities such as the World Health Organization, the Royal Society and the US National Academies. In the case of the 14-day rule, we still have a chance to get ahead of the science. □

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