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Considerations for the future of in vitro gametogenesis in fertility care

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The potential use of in vitro gametogenesis (IVG) as a reproductive technology could redefine parentage, including the possibility of bipaternal parentage, raising hopes for those who have infertility or desire reproductive autonomy. However, IVG is not yet feasible for human reproduction, and substantial hurdles must be overcome if it is to become a clinical reality. This Comment outlines the major technical limitations of IVG and argues for public engagement in shaping the future directions of IVG research.

The need for new reproductive technologies is severe and pressing. According to the World Health Organization, 1 in 6 people experience infertility in their lifetime[1]. Infertility is defined as the inability to become pregnant after 12 months of trying and is associated with disease or damage to the reproductive or endocrine system. Infertility is treatable in some cases with a personalized plan that could involve lifestyle changes, medications, surgery or assisted reproductive technologies such as in vitro fertilization (IVF). Despite this, many people are still unable to start or build families. For people who do not generate gametes, people whose gametes result in non-viable embryos, or same-sex couples who want to share genetic parentage, there are no options for having a biological child with current reproductive technologies. In these cases, in vitro gametogenesis (IVG) could fill a gap in family building. Yet the science for making a human gamete in the laboratory must first overcome the major obstacle of low gamete and embryo quality seen in both animal testing and human embryo research before clinical use can be considered.

IVG with mouse cells

IVG is the differentiation of germ cells outside of the body[2]. This singular goal has been met with multiple approaches. Most researchers start with pluripotent stem cells (PSCs), so that the entire process of germ cell development occurs in the laboratory. Another strategy involves transferring unreplicated diploid somatic chromosomes into metaphase II oocyte cytoplasts using somatic cell nuclear transfer (SCNT)[3]. In this approach, a donor oocyte is required to make a gamete. To generate an embryo, the IVG-derived gamete made with differentiation of PSCs or through SCNT is fertilized using a gamete of the opposite sex. To date, IVG success has been shown using mouse cells, including the generation of embryos and live births. However, a major challenge is that IVG gametes make poor-quality embryos, and fertilization of IVG-derived gametes made from mouse cells results in a high incidence of miscarriage and low frequency of live births[4–10]. Understanding where IVG cells go awry in animals such as mice could provide clues to mitigate these same problems with human cells[11].

Starting with mouse PSCs, fertilization-competent mouse oocytes are generated in around 2 months when in vitro-derived germ cells are combined with embryonic-stage ovarian somatic cells in an organ-culture-like environment[4–6]. To demonstrate live births, hundreds of embryos generated from PSC-IVG have been transferred across many reproductive-age female mice to generate a very small number of live-born pups. For SCNT-derived oocytes, the gamete is generated in a day, instead of months, making the SCNT-IVG approach more compatible with current clinical practice. Yet, like PSC-derived gametes, SCNT-IVG embryos exhibit a high incidence of abnormality when fertilized[10,12] and very low live birth success rates, even when transferring only good-quality embryos[10].

The reasons behind the low-quality eggs and embryos from IVG are many. For PSC-IVG, the resulting gamete exhibits incomplete epigenetic reprogramming, errors in meiosis and fertilization failure[4,5]. For SCNT-derived oocytes, random mis-segregation of somatic chromosomes to the polar bodies leads to chromosomal abnormalities in the resulting fertilized eggs and embryos[10,12]. Therefore, IVG with mouse cells, although promising, will benefit from more research to identify corrective and preventative measures aimed at improving gamete quality. Low quality gametes that lead to high incidence of miscarriage will be a major factor that prevents even the consideration of human IVG for use in reproductive medicine.

The path forward will require fundamental changes to the practice of IVG with hypothesis-driven science based on understanding what is going wrong so that strategies can be developed to improve the protocol. For PSC-IVG, this includes improvements to the gonadal somatic cell differentiation and germ cell specification protocols so that germ cell–somatic cell interactions are appropriate. SCNT-IVG will need a strategy that prevents the random assignment of chromosomes to the polar body. Both technologies will also benefit from more sensitive, non-invasive screening tools to identify good-quality eggs and embryos. IVF in the reproductive medicine clinic will also benefit from such tools.

IVG with human cells

Human IVG with human PSCs is still a work in progress; fertilization-competent gametes have not yet been achieved by researchers. Instead, what is currently possible with PSC-IVG is the differentiation of immature oogonia or pro-spermatogonia in approximately four months of differentiation when combined with mouse embryonic somatic support cells in xenogeneic reconstituted testes or ovaries[13,14]. Improvements on this initial success involve the use of extended culture system on mouse fibroblast support cells in media containing bone morphogenetic protein 2 and other additives[15]. The next stages of PSC-IVG will be the most

challenging, requiring the complex process of meiosis. There is hope that human germinal vesicle-stage oocytes will be generated without the use of any mouse cells given recent success using chemically defined media to generate oocytes from mouse PSCs[16]. Attempting this with human PSCs will first require identifying key signaling pathways generated by gonadal support cells that induce the progression of oogonia or spermatogonia through meiosis.

In contrast to human PSC-IVG, human SCNT-IVG is closer to the clinic because gamete differentiation is not needed. Instead, SCNT-IVG uses donor gametes, with the source of donor eggs a critical ethical consideration given concerns with financial reimbursements and the potential for commodifying eggs if demand is high. The process of generating a gamete using SCNT-IVG (a technology that has been dubbed mitomeiosis) takes less than a day once the donor human oocytes and G0/G1-arrested human somatic cells are available[3]. Once the spindle–chromosomal complexes are removed from the donor human oocytes, the oocyte cytoplasts are fused with the G0/G1-arrested fibroblasts and fertilized with sperm using intracytoplasmic sperm injection. Assisted activation using electroporation and the cyclin-dependent kinase inhibitor roscovitine results in ~8% of fertilized SCNT-IVG oocytes reaching the blastocyst stage. However, all SCNT-IVG human embryos are aneuploid and none of the maternal genome has undergone homologous recombination, which is a standard requirement for meiosis in human eggs[3].

The generation of human embryos following IVG

Once a human gamete or embryo is made using IVG, the next major biotechnological challenge will be determining quality and mitigating unwanted outcomes such as failed pregnancies, repeated miscarriages or birth defects. In the IVF clinic, preimplantation genetic testing for aneuploidies has not improved live birth rates[17]. Similarly, deep learning morphology-based embryo selection has also not improved clinical outcomes[18]. Preimplantation genetic testing for aneuploidies will detect chromosomal problems, but, given that transfer of morphologically high-quality embryos still results in >90% miscarriages, additional features like epigenetic reprogramming should also be assessed. Our focus groups suggest that generating large numbers of embryos for testing and discarding is not desirable to many participants[19].

Given the ability to generate embryos with IVG, various organizations have sought to establish regulatory frameworks or host workshops to discuss research and clinical use of the technology[20,21]. While some organizations are focused on local jurisdictions, the International Society for Stem Cell Research is actively involved in creating a global framework informed by, and in collaboration with, various organizations across the world through their Guidelines for Stem Cell Research and Clinical Translation. The last IVG update to the guidelines[22] was in 2021. Since then, SCNT-IVG was developed and human embryos have been generated[3]. In addition, there has been considerable commercial investment in IVG for reproductive purposes, accompanied by reduced transparency concerning research funders and publication practices that may be limited by proprietary motivations. This worrisome development highlights the need for cross-sector coordination and communication to establish updated regulatory standards that do not differ across academic and commercial settings, with international harmonization to enable collaborative, transparent science for clinical applications.

IVG for human reproduction and family building

IVG should only be considered for human reproduction once all safety concerns are addressed and ethical considerations fully explored. For researchers, IVG with human cells is currently subject to a patchwork of cross-jurisdiction differences. In the United States and most parts of the world, PSC-IVG is relatively straightforward and follows the same regulatory framework as other human PSC projects, including human subject research and institutional approvals. However, when PSC-IVG gametes are used for fertilization, used for parthenogenesis or involve donor gametes, such as in SCNT-IVG, the technology enters the complex landscape of laws and policies that govern research with donor human gametes and embryos[23]. Frameworks for human embryo research differ extensively across the United States and in different regions of the world. For example, in jurisdictions with policies prohibiting research on fertilized eggs and embryos (for example, Germany) or the generation of human embryos for research purposes (for example, California), it is likely that PSC-IVG gametes cannot be fertilized or made into embryos for research.

For SCNT-IVG, the rules are even stricter. Many jurisdictions ban SCNT completely, even for research purposes (for example, Michigan, Missouri and nine other states)[23], making SCNT-based IVG a nonstarter in many places. The United States Food and Drug Administration, which would evaluate safety of IVG before it could be used for human reproduction in the United States, currently does not acknowledge receipt of projects that involve genome modification of the germline. A recent report from Nuffield Council on Bioethics and the Future of Human Reproduction raised the question as to whether gametes and embryos made via IVG should have the same status as gametes retrieved from the body. Public engagement on this issue, inviting the input of people with lived experiences of infertility, has demonstrated how a thoughtful and engaged public can expand the regulatory and scientific conversation in important ways[24].

There is a path forward for stronger, unified publicly informed regulation of IVG research: include IVG in the same contemplative, public-engaged process being undertaken for stem cell-based embryo models and the culture of human embryos for research purposes. Responding to a wave of interest in using embryos in research, the United Kingdom has taken the lead in proposing a 28-day culture limit to create technologies to improve fertility care, identify causes of birth defects, or provide answers to those people who experience early pregnancy loss[25]. Stem cell-based embryo models designed as experimental tools with which to improve on existing reproductive technologies, and as entities with likeness to human embryos, are included in the discussion with the aim of creating a regulatory framework for both. Overlooking IVG models in publicly engaged dialog about human embryos and embryo models misses an opportunity to connect with stakeholders on IVG for reproductive purposes and family building.

Conclusions

Infertility is a major problem that requires scientific solutions. IVG is a technology that touches on the most sensitive ethical issues that we face in human reproduction, from questions of responsibility for safety to implications of new forms of biological continuity between generations. Investment in the discovery phase of IVG, whether it gets all the way to the clinic or not, will make fundamental contributions to our understanding of human reproduction. This research rightly comes with complex regulatory and policy requirements that researchers in the field must navigate if embryos are to be made, regardless of whether the goal is use as a scientific model or a reproductive technology. The social value of IVG for reproductive purposes may conflict with ethical concerns over the moral status of embryos, personhood laws, affordability and accessibility. At the same time, IVG elicits hope for more routes to genetic parentage and reproductive autonomy, particularly among those who cannot generate viable gametes or are

otherwise underserved by current reproductive technologies[19]. Clear regulatory frameworks for researchers informed by ethics, meaningful and regular public engagement, and more cohesive policies will make navigating this complex landscape easier while providing a path forward to increase family-building options.

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A.T.C. and H.L.L. wrote the manuscript collaboratively.

Competing interests

A.T.C. is on the board of directors of the International Society for Stem Cell Research.