Nuffield Council on Bioethics

future of human reproduction

INTERDISCIPLINARY RESEARCH

POLICY BRIEFING

In vitro gametogenesis

Ethical and policy questions

Summary

- In vitro gametogenesis (IVG) is a technology which aims to create viable human eggs and sperm (gametes), grown from either embryonic or induced pluripotent stem cells (e.g. skin cells) in a laboratory.
- IVG is not currently in clinical use, but research in non-human animals is advancing and the possibilities that IVG could offer for human reproduction are potentially transformative.
- This policy briefing focusses on potential clinical applications of IVG in the future, and the associated ethical, legal and social issues these raise.
- IVG may bring significant benefits for addressing infertility and enable a wider range of people to have their own genetically related children – such as enabling same-sex couples to have a child genetically related to both parents.
- IVG raises a range of ethical issues, including around consent, the role of genetic relatedness in families and equity of access to such treatments should they become available.
- The law currently prohibits the clinical application of IVG, but IVG research is permissible within the current UK legislative framework.
- Before direct application of IVG to human reproduction can be considered, rigorous testing will be needed to ensure its safety, alongside extensive public engagement and a thorough consideration of the ethical and legal issues.
- If deemed sufficiently safe, and ethically and socially acceptable, changes to existing legislation would be required before IVG could be used in the clinic.

Introduction

In vitro gametogenesis (IVG) has the potential to transform human reproduction by providing new ways to become a genetic parent. Although clinical applications of IVG are not on the immediate horizon, significant advances in research suggest that it is timely to consider the scientific, ethical, and legal questions surrounding their potential use.

Gametogenesis is the process by which eggs and sperm (gametes) develop, from their origin as stem cells in the early embryo, into mature gametes capable of fertilisation. In vitro gametogenesis aims to replicate this process outside of the human body to produce *in vitro derived gametes* (IVD gametes).

Scientists are able to create pluripotent stem cells, which have the potential to develop into any cell of the body, through 're-programming' cells taken from tissue such as skin or from blood. In the laboratory, methods have been developed to grow mouse stem cells into eggs which have been fertilised to produce apparently healthy offspring. However non-human primate and human IVG research is less advanced and significant challenges remain, for example with respect to our understanding of how gametes develop within the body, and how to replicate these conditions in the laboratory, as well as how the quality of developing IVG gametes might be assessed. While research is developing at a rapid pace, there is no consensus on the likelihood of achieving successful IVG in human reproduction or on how soon this might occur.

This policy briefing sets out the key scientific, ethical, and legal issues raised by potential future uses of IVG in human reproduction, with a focus on issues that would need to be addressed before IVG might be introduced to the clinic.

Whether IVG will one day become part of human reproduction or not will depend not only on scientific developments, but on the social and ethical acceptability of the practices that it may make possible. Given that those working in the field have made predictions about its feasibility in human reproduction, even within a decade, it is prudent to consider now the questions that IVG raises.

Potential clinical applications of IVG

If IVG research is successful, and its safety and efficacy become well-established, then it will have the potential to make some important differences to clinical practice.

First, it could **improve and expand the coverage of current infertility treatment**. IVG may enable those currently unable to produce gametes to do so – and it could, for example, be used for fertility restoration where people are undergoing cancer treatments that threaten their future fertility. It could also be used to enable older people (in particular, older women) to produce their own gametes beyond their biological fertile years.

IVG could drastically reduce the number of donated gametes needed in fertility treatment, since it will be possible to create eggs or sperm from the patient's own cells, meaning that no donor is required. Similarly, IVG could provide an alternative to current egg retrieval practices for mainstream IVF – potentially becoming easier, cheaper, and less burdensome for the patient.

IVG may also **allow new types of biological family to emerge**. For example, same-sex couples could both be genetically related to their children (though, in the case of two males, a surrogate would still be needed). There has also been speculation about the possibility of children who have three or more genetic progenitors, and about 'solo' reproduction, where both gametes come from the same person. It should be noted, however, that 'solo' reproduction in particular would raise serious safety, health, and ethical concerns and is unlikely to be accepted or allowed in the foreseeable future.

Finally, IVG could potentially be used to **expand existing embryo selection practices**. It could vastly increase the number of embryos available to clinicians and prospective parents. This, combined with advances in genomics, may lead to an expansion of the scope of preimplantation genetic testing (PGT), which currently involves checking embryos for specific genetic traits or conditions before they are used in fertility treatment.

Ethical considerations

The prospect of IVG being used in human reproduction raises a diverse range of ethical questions, relating to their moral and legal status as well as possible uses and wider impacts.

For example, there are questions about the status of embryos created from IVD gametes ('IVG embryos'). Would their status scientifically and morally be the same as that of other embryos or are they a different kind of entity? Should they have the same protections as other embryos? How might or should these entities fit into regulatory frameworks and how should they be classified?

There are also fundamental questions about safety and the wellbeing of any children born as a result of fertility treatment using IVG. For example, what level of risk is acceptable when testing new reproductive techniques on human beings and what level of evidence would we need beforehand to render such tests ethically acceptable? How is the value to a prospective parent of having their own genetically related child to be factored into cost-benefit calculations?

Turning to IVG's capacity to create novel family forms, many will view this as a welcome development, increasing options and increasing equality. For example, enabling same-sex couples to have genetically related children may be viewed as positive because it allows those families to have the same access to genetic relatedness as many others. On the other hand, it could be argued that using IVG in this way further entrenches biological and/or genetics-based view of families.

Other possibilities, such as creating children with three or more genetic progenitors, or deriving both sperm and egg from the same person so that that person is the child's sole genetic parent are likely to be more contentious and raise significant questions such as whether these reproductive aspirations justify the potentially higher costs and risks involved.

Finally, as noted above, the potential of IVG to enable far higher levels of embryo selection is often highlighted as a site of ethical debate. While, on the positive side, enhanced selection capabilities may lead to a reduction in the prevalence of serious genetic disorders and offer prospective parents more choice, they also raise concerns. These include: what the unforeseen consequences of extensive embryo selection might be; whether IVG and selective technologies might be used for 'eugenic' purposes or have negative impacts for people with disabilities; and whether IVG and selective technologies could be used to select traits other than those related to health (e.g. relating to appearance, or 'enhancements').

Legal and policy considerations in the UK

There are questions about how current governance and regulation frameworks in the UK might apply to IVG. Oversight from both the Human Fertilisation and Embryology Authority (HFEA, the body that regulates assisted reproduction and embryo research in the UK) and the Human Tissue Authority (HTA, the body which regulates the removal, storage and use of human tissue for research, medical treatment, education and training) may be needed.

IVD gametes and embryos created using them (IVG embryos) cannot currently be used in assisted reproduction under the amended Human Fertilisation and Embryology Act 1990 (HFE Act) because they would not satisfy the definition of 'permitted' gametes and embryos for use in treatment. However, the general definitions of eggs, sperm and embryos in the HFE Act could be interpreted to include IVD gametes and IVG embryos, meaning that IVG research would be permitted and regulated by the HFEA. In this case, the 14-day limit on embryo research would also apply, which could prove problematic because establishing the safety and validity of IVG embryos would likely require sustaining IVG embryos past this point in time.

Recently, the HFEA suggested updating the law to take account of future developments such as IVG. It is important to consider what any update could or should involve, including which uses of IVG (if any) should be permitted, if it were to be deemed safe and ethically acceptable. Legal updates could include provisions to explicitly regulate research involving IVD gametes and IVG embryos, as well as their use in treatment. This could take the form of amendments to primary legislation (the HFE Act), and/or the introduction of a power to make regulations (secondary legislation) as occurred in the case of mitochondrial donation treatment.

Consent

If IVG were deemed appropriate for use in assisted reproduction, policymakers would need to determine an appropriate consent framework. Considerations include the HFEA's recent recommendation that the current consent processes for assisted reproduction in the UK require simplification, as well as:

- Whether to amend the law governing consent in assisted reproduction to allow for specific consent requirements, e.g. mandatory counselling for using IVG in reproductive treatments.
- Whether individuals who donate IVD gametes need to consent to the disclosure of their information or identity to people conceived using those gametes.
- What rights children born of IVD gametes should have regarding knowledge of their genetic origins.
- How concerns about gamete theft can be addressed. For example, should taking cells to create IVD gametes without consent be a specific criminal offence?
- Whether people who provide tissue for IVG research or IVD gamete donation follow the same consent regimen as current gamete and embryo donors.

Parenthood

Policymakers must also consider how some uses of IVG may disrupt current legal provisions regarding parenthood. For example, although a birth mother's legal status is unlikely to be affected by the use of IVG, it could allow for more complex parenting scenarios to emerge, raising new questions regarding parenthood.

If IVG is permitted for use in human reproduction, possible questions may include:

- In multiplex parenting, where three or more genetic contributors would be involved, who would be the two legal parents of any resulting child, or should the law be reformed to recognise more than two legal parents?
- If an unmarried same-sex couple used IVG to have a child that is genetically related to them both, how could they ensure that they would both be legal parents?
- In a scenario where someone's cells are taken without their consent to create IVD gametes, would they be a legal parent of any resulting child?

Child welfare

If IVG is approved for clinical use and specified as an activity which can be authorised by a licence, it would be subject to the licence conditions under the HFE Act. This would include the duty to consider the welfare of any child who may be born as a result of treatment and of any existing child(ren) of the family.

Existing fertility treatment centres, experienced in a diverse range of cases, may be well suited to address welfare concerns related to IVD gametes and IVG embryos. Important questions to consider with respect to welfare include:

- Will novel physical or psychological risks be presented by the use of IVG?
- What, if any, possible discrimination might future children face relating to the role of novel reproductive technologies in their conception and family formation?

Funding and access

There are well-recognised concerns about access to publicly funded fertility treatment in the UK, and IVG could introduce further complexities around how NHS resources are allocated and who can access treatment. Policymakers will need to deal with these challenges. Issues to address include:

- Whether IVG should ever be a candidate for NHS funding.
- The long-term effects of not publicly funding IVG, meaning that it was only available to those who could afford to pay.
- Whether IVG is different from other fertility treatment services, many of which currently receive limited public funding.
- The role of intellectual property rights in shaping access to IVG.

Looking ahead

IVG has the potential to provide new treatment options for people seeking fertility treatment and to create new types of biological families. However, it may also challenge existing norms and raise ethical and social questions relating to safety, consent, and the wellbeing of children and families.

As laboratory research continues to advance, scientists, ethicists, and policymakers should work together to consider the novel questions the use of IVG would raise, as well examining the current legislative and governance limits. Cross-disciplinary collaboration, ethical deliberation, wider public debate, and informed policymaking is needed to ensure the responsible development of this technology and possible clinical use.

This policy briefing draws on a report produced as part of a two-year collaboration between the Wellcome-funded Future of Human Reproduction Project (222858/Z/21/Z) and the Nuffield Council on Bioethics (NCOB). The report was researched and co-drafted by Sara Fovargue and Laura O'Donovan (both FoHR and School of Law, University of Sheffield), Stephen Wilkinson and Nicola Williams (both FoHR and School of Global Affairs, Lancaster University) and Ranveig Svenning Berg (NCOB).

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