The Ethical Challenges of Radical Innovations in Assisted Reproduction

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Introduction

In the past decade, society has witnessed several radical innovations in assisted reproduction that have caused immense ethical, regulatory, and public debate worldwide. Mitochondrial replacement techniques (or '3-person IVF') in the form of maternal spindle transfer were used to create offspring for the first time in 2016, in Mexico (Zhang 2017). The lead clinician, Dr. John Zhang, explained that the procedure was carried out in Mexico because 'there are no rules' (Hamzelou, 2016). In November 2018, a Chinese scientist named Dr. He Jiankui announced that he had gene-edited twin embryos, which had resulted in the twin birth of girls in October 2018 (Cyranoski 2019). Scientists and ethicists immediately condemned this 'experiment' by Dr. He as 'monstrous' and irresponsible (Cyranoski 2019). However, despite these controversies, radical innovation in assisted reproductive science and medicine has shown no signs of slowing down, let alone stopping.

For example, work on in-vitro derived gametes[1] continues to progress faster than many expected. Scientists have developed promising living 'proof of principle' mouse specimens (Hayashi et al. 2012; Hikabe et al. 2016), and positive results have been obtained with in-vitro research using human cells (Yamashiro et al. 2018). If in-vitro derived gamete techniques become adequately reliable, then we will no longer need gamete donation. In theory, in-vitro gametes could also make it possible for same-sex couples could have children to whom they are both genetically related (with nuclear DNA) (Li et al. 2018). Considerable progress has also been made in developing ectogenesis technologies, also known as 'artificial wombs,' which would allow fetal gestation outside the human body. To date, 'biobag' models for ectogenesis have demonstrated success in gestating premature lambs (Partridge et al. 2017). In October 2019, it was announced that a Dutch research team was awarded 2.9 million euros to develop a prototype ectogenesis technology for humans (Davis 2019). These emerging techniques raise serious ethical, regulatory, and scientific questions for the future generations of offspring they might create.

[1] Also known as artificial gametes, stem cell-derived gametes, and synthetic gametes.

Innovations such as the ones mentioned above are radical by nature because they are a significant departure from any standard practice, and they are different in ways that make them unique. However, what makes them unique is also what makes them ethically contentious and disruptive. They disrupt the language we have become accustomed to using in our debates. They disrupt our understanding of the significance and meaning of genes, genetic relatedness, and the way we think about our genetic constitution. They disrupt our normative ideas of family. They disrupt how we think about safety and the costs of translating radical innovations from bench to bedside. They also can disrupt our trust in scientific innovation. Therefore, what are we to make of all this disruption?

In light of these developments and disruptions, I ask the following question: what are some of the key ethical challenges presented by radical innovations in assisted reproduction and, when possible, how should these challenges be addressed? My response to this question aims to take into account Article 16 (Protecting future generations) of the UNESCO Declaration on Bioethics and Human Rights, which states that 'the impact of life sciences on future generations, including on their genetic constitution, should be given due regard' (UNESCO 2005, Article 16).

While the number of ethical challenges that emerge with the radical innovation of reproductive technologies is too numerous to address in one piece of work, I aim to address a set of four critical areas of concern in this chapter. First, I make some terminological clarifications surrounding the use of the term 'radical innovation' in assisted reproduction. Second, I argue that the emergence of radical innovations in assisted reproduction requires that we take a more nuanced approach to use the word 'parent' to ensure that future ethical debates and regulations are precise and meaningful. This is crucial if the aim is to develop effective ethics and regulations to protect future generations. Third, I argue that radical innovations in assisted reproduction, such as in-vitro derived gametes, have disrupted our traditional concepts of 'genetic relatedness' and our perception of future offspring's genetic constitution. Fourth, I argue that radical innovation in assisted reproduction presents society with a range of safety risks and costs and the promise of decreasing suffering and ultimately making reproduction safer. However, I argue that society has a responsibility to ensure that the introduction of radical innovations is translated from bench to bedside to prioritize the safety and welfare of future generations (and their parents) and foster trust in science.

Part 1: What is a 'radical innovation' in assisted reproduction?

To begin, I wish to make some terminological clarifications. In this chapter, I focus specifically on the ethical challenges of ‘radical innovations’ - not merely ‘novel’ practices and technologies or anything that might only constitute an 'innovation.' The Oxford English Dictionary (OED) can help get to the essence of the matter. According to the OED, 'innovative' refers to something 'featuring new methods; advanced and original' (OED 2019a) and ‘novel’ refers to something ‘interestingly new or unusual’ (OED 2019b). While this language helps point out something different, it does not seem to adequately characterize or make a distinction between: a) an incremental but unique advance in a field; and b) a breakthrough that does something fundamentally different from what previously existed in that field. For example, a drug company may release an existing painkiller tablet in a new ‘time-release’ format, which is novel and innovative for that particular painkilling drug. However, there may be nothing ‘fundamentally’ new about using that ‘time-release’ technology that already exists in other drug capsules or elsewhere in medicine.

In contrast, radical innovations in assisted reproduction, such as gene-editing, in-vitro derived gametes, mitochondrial replacement techniques, and ectogenesis, are more than merely ‘innovative’ or 'novel' technologies, and such adjectives do not appear to describe the uniqueness that makes these technologies so significant and disruptive. According to the OED, one meaning of radical is ‘relating to or affecting the fundamental nature of something; far-reaching or thorough’ (OED 2019c). Therefore, it appears that calling the above technologies[2] ‘radical innovations’ would go some way towards encapsulating a description of how they are fundamentally new and original advancements by their very nature. For example, mitochondrial replacement techniques are the first technology to combine the DNA of three people (two nuclear DNA contributions and one mitochondrial DNA contribution) to create an embryo. Similarly, ectogenesis would fundamentally change reproduction by allowing humans to develop from ‘embryo to infant’ outside the human body.[3] CRISPR/cas9 gene-editing tools allow scientists to edit the human genome with ease and efficiency never witnessed before. The above examples are among the first of their kind, and each represents a radical and fundamental departure from standard practice in assisted reproduction.

[2] Other 'radical innovations' in assisted reproduction include, but are not limited to synthetic embryos, synthetic human entities with embryo-like features (SHEEFs), genetically edited embryos, and reproductive organoids.

[3] An excellent publication by the Nuffield Council on Bioethics (2012) on emerging biotechnologies also points out that their 'transformative potential' may also characterize the types of technologies I refer to. While I do not have the scope to explore this in further detail in this paper, future work in this area would benefit from expanding on this report's work and the detailed insights it contains.

Distinguishing the ‘radical’ from the ‘innovative’ or ‘novel’ is not merely an administrative point or a linguistic quibble. It is a difference that requires us to consider two key points when evaluating such technologies from a scientific, ethical, or legal point of view. First, making the distinction between an ‘innovation’ and a ‘radical innovation’ requires that an additional deliberative step is taken to articulate precisely how an innovation is or is not fundamentally different from existing assisted reproductive technologies.[4] This deliberative step necessitates that we identify the key differences, which then enables us to be specific about why these fundamental differences matter from an ethical or legal point of view (amongst others). Second, the language of 'radical innovation' allows us to ensure that such innovations are not equivocated in our regulations with other instances of regular innovation. Radical innovations may require radically new regulations or approaches. By taking a moment to recognize that these radical innovations in assisted reproduction are, in fact, 'exceptional,' we also provide ourselves with the opportunity to pause and consider whether our existing ethical approaches and regulatory policies are fit to govern them. Therefore, this language is purposeful because it helps to hold us to account and take these ‘radical innovations’ seriously.

Part 2: What do we mean when we say ‘parent’?

With the emergence of radical innovations in assisted reproduction, there has been considerable controversy surrounding how these innovations might affect our current concepts of 'parent.' According to Brake and Millum (2018), at least five distinct senses of the term ‘parent’ are used in philosophical and legal literature: moral, legal, social, biological, and genetic. I argue that these concepts of ‘parent’ are a good start but need to be added to if we aim to have an accurate ethical and regulatory debate about assisted reproductive technologies.

The term ‘biological parent’ has traditionally been used to refer to a progenitor who contributes approximately 50% of the nuclear DNA to creating a child. However, the emergence of (non-genetic) gestational surrogacy in the 1980s made it possible for surrogates to be considered biological parents while not having a genetic link to the child. Therefore, while both surrogates and progenitors are biological parents, only the progenitors are also genetic parents.

The distinction between biological parents and genetic parents worked well before the emergence of mitochondrial replacement techniques. However, mitochondrial replacement

[4] This point is meant to counter claims that are occasionally heard in the recent UK and USA debates over how to regulate mitochondrial replacement techniques. Some attempted to argue that mitochondrial replacement techniques were just 'fancy IVF' and did not warrant further scrutiny. Scientifically and ethically speaking, this claim is fundamentally incorrect.

techniques complicated matters by creating offspring with genetic contributions from at least three people: two gamete donors (who contribute nuclear DNA) and a third gamete donor (who acts as a ‘mitochondrial donor’ and contribute mitochondrial DNA). All three are ‘biological parents’ by virtue of having contributed some biological materials to create the embryo. Similarly, all three are also ‘genetic parents’ by virtue of having contributed some genetic materials (albeit different genetic material) to create the embryo. However, using the term ‘biological parent’ or the term ‘genetic parent’ would seem to falsely equivocate the contributions of each person's reproductive materials. Instead, a distinction should be made about whether a parent is a 'mitochondrial genetic parent' or a 'nuclear genetic parent.'

In the UK, as is the case in many countries, having offspring via a licensed fertility clinic will result in the parents who are intending to have the child – the ‘intending parents’ - being considered the ‘legal parents’ (UK Human Fertilisation and Embryology Act 2008, as amended). It may be the case that these legal parents are also viewed as 'social parents' responsible for caring for their offspring. However, these concepts of parenthood need to be broken down further. We know that the legal parents of offspring are not always socially responsible for them (e.g., it could be another family member, friend, or carer), so the link between legal parents and social parents cannot always be assumed. Furthermore, offspring may have parents engaged in parenting activities for them – 'engaged parents' – but it may nevertheless be the case that the offspring do not recognize them as their parents (i.e., as 'recognized parents'). This is especially true in assisted reproduction cases where donor-conceived offspring sometimes feel that their 'recognized parents' are their donors (or ‘genetic parents’), despite those donors not necessarily being their social parents or legal parents. As radical innovations in assisted reproduction continue to add new concepts of 'parent' to our list and disrupt parental roles in relation to offspring, ethicists and regulators must be specific about the concepts of ‘parent’ in use within any discussion.

Of course, one of the other important projects that ethicists and regulators must undertake when presented with radical innovations in assisted reproduction is determining whom the parent or parents morally responsible for the new generations of offspring created are. Thus, moral parenthood theories are used to situate the locus of moral responsibility on a specific type or types of parent. Some common moral theories of parenthood include causal accounts, intentional accounts, labor-based accounts, and biological accounts (which include genetic accounts). However, to apply these theories to any situation accurately, it is essential to determine the types of parent in that situation. This is because some moral theories of

parenthood will place moral responsibility with some parent types, but not others. For example, biological accounts of moral parenthood that place heavy emphasis on the nuclear genetic ties between parents and offspring also argue that the offspring's genetic parents are the parents that bear moral responsibility for those offspring. By being very specific about the concepts of 'parent' that are relevant and in use - in any debate or theory - we can ensure that moral theories of parenthood are applied more precisely in ethics and regulatory contexts going forward.

Part 3: What is the significance of genetic relatedness, and how should we think about the offspring's genetic constitution?

As the above discussion on 'parents' indicates, the notion of 'genetic parent' becomes increasingly problematic in the context of radical innovations in assisted reproduction. In this section, I explain how radical innovations create challenges for some of how society has become accustomed to thinking about genetic relatedness and the genetic constitution of future generations.

Increasing scientific progress with in-vitro derived gamete technologies[5] is likely to present unique benefits to assisted reproduction, as well as challenges to the genetic constitution of future generations. Creating in-vitro derived gametes involves culturing human stem cells in-vitro into gametes, and these gametes can then be used to create human embryos. The potential benefits of this radical innovation are enormous. For example, it could solve shortages of gamete donors for both research and assisted human reproduction. This could be incredibly valuable in ethnic and religious communities where having genetically related children is essential or where having children without a genetic tie is problematic or stigmatized. In-vitro derived gametes also offer the prospect of no longer requiring that donors – especially women – be put at risk (via oocyte harvesting) or inconvenience to fulfill society's demand for gametes (Cutas and Smajdor, 2015).

However, there are concerns about how in-vitro derived gametes could result in some unusual reproductive scenarios. For example, it might be possible to continuously derive many successive lines of gametes in-vitro, each representing a new genetic generation. This could be done by deriving gametes from stem cells provided by living human donors and then combining pairs of these gametes to create a line of embryos. New gametes could then be derived from the stem cells taken from this first line of new embryos. These new gametes could

[5] For a more detailed account of the different methods used to create in-vitro derived gametes, see Smajdor and Cuts 2015.

then be crossed with other in-vitro derived lines of gametes that had undergone the same process. After repeating this cycle of deriving gametes and embryos enough times, it is possible to create embryos are no more 'genetically related' to their original living human stem cell donors (what we could refer to as a 'causal parent') than any other random stranger that you might find on the street. In this situation, it would be the case that the offspring's nearest genetic relatives are the most recent embryo lines that they were derived from in-vitro. These 'genetic orphans', as Sparrow calls them, would have no genetic parents in the conventional sense – at least no genetic parents that existed as anything other than embryos (Sparrow 2014).

Here it is worth pausing to highlight an interesting point that emerges from the in-vitro derived gamete debate. So far, research on in-vitro derived gametes has come under intense criticism because it is argued that these technologies are primarily aimed at allowing infertile people to create gametes that will allow them to have children to whom they are genetically related (Smajdor and Cutas 2015). Following this criticism, it is argued that society should be moving away from placing so much emphasis on having children with genetic ties to their parents and that these technologies are problematic because they move social attitudes in the wrong direction by emphasizing that genetic ties are important (Smajdor and Cutas 2015). Critics who are proponents of this view go on to argue that it is not worth the costs or the potential medical risks to develop and use these technologies just for the sake of creating genetic ties between parents and offspring (Smajdor and Cutas 2015).

However, the case of 'genetic orphans' challenges this logic. Rather than reinforce the value of genetic ties between progenitors and offspring, in-vitro derived gametes have the potential to sever the genetic-tie in a way that has never been done before and turn the entire debate on its head. The question that emerges is the following: if you cannot have a genetic tie with your own children, is it still preferable to have children that *are at least not genetically related to anyone else*? What might the ethical implications be for the resulting offspring? Why might intending parents value having offspring with such a genetic constitution? Unfortunately, I cannot take up these questions in this chapter, as it requires a much larger discussion; however, these are questions that deserve further exploration as the development of technologies such as in-vitro derived gametes progress.

The possibility of using in-vitro derived gametes to create 'genetic orphans' raises critical ethical questions about the significance of the genetic makeup of any future generations we create using radical innovations in assisted reproduction. For example, some people place value

on tracing (and in some cases meet) their progenitors because they feel it is vital to develop an integrated narrative sense of self (Brock 2002). Genetic orphans would be unable to identify a living nuclear genetic parent that they share 50% of their genetic information. Therefore, this could frustrate their desire to satisfy the potential interest in developing this notion of 'sense of self.' Depriving offspring of a conventional narrative of genetic ancestry would likely be viewed to be morally impermissible by some philosophers, like Velleman (2018). They have argued for the importance of such a narrative for offspring for their ability to flourish. As Ravitsky argues, research on donor-conceived offspring (as the nearest comparison) indicates that some offspring certainly do want to know who their progenitor is, and they would like to know this in order to understand this ancestral relationship and perhaps also (in some cases) meet their donor (Ravitsky 2010). However, Ravitsky points out that meetings do not always go as planned, and parental relationships do not always materialize (assuming the donor can be located) (Vardit 2010).

Genetic orphans may also have medical concerns due to the nature of their genetic heritage. Typically sperm or egg donors have family histories taken alongside standard medical screening tests at fertility clinics to identify any inheritable disorders that could be passed on to offspring. However, genetic orphans would lack recent ancestors who have reported if they had experienced any genetic-based medical problems during their lives. Instead, clinicians would only have the genetic data from screening the in-vitro derived gametes and resulting embryos. Therefore, consideration should be given to whether any future generations conceived as genetic orphans would potentially suffer due to the worry that their genetic constitution might leave them vulnerable to unknown medical complications. Of course, it is also possible that these in-vitro derived gamete techniques could allow clinicians to engineer[6] (potentially with the use of gene-editing technology) (Sparrow 2014) the genetic constitution of future generations in a way that reduces medical risks and benefits any offspring created (regardless of whether or not they are genetic orphans).

Part 4: The safety and costs of radical innovations in assisted reproduction

This section of the chapter touches on two significant challenges that require further research and reflection with the emergence of radical innovations in assisted reproduction. The first challenge is the importance of safety and how regulators and ethicists must recall that our options of how to 'safely' use radical innovations are different now than they were when

[6] Sparrow has identified the concern that this could result in 'in vitro eugenics.'

Steptoe and Edwards were successful with IVF in 1978 (Steptoe and Edwards, 1978). The second challenge is the idea of 'cost'. What costs are society willing to tolerate in exchange for allowing radical innovations to move from 'bench to bedside'?

Debates about safety always occupy most of any discussion surrounding the development and clinical introduction of radical innovations in assisted reproduction. However, protecting future generations against safety risks is incredibly complicated in cases of radical innovation. Often offspring are being created in what is a 'world first' situation. In the 1970s, when Steptoe and Edwards worked on IVF, the regulatory setting was much different, but still surprisingly ethically stringent (Johnson and Elder 2015). According to the Oldham Notebooks (archival records from Steptoe and Edward's work on IVF), one of the 'safety' mechanisms put in place to protect against unwanted IVF outcomes surrounding the gestation of the baby was that if it emerged that the baby showed signs of a congenital disability the parents had agreed that the baby would be aborted. In an article on the ethical dimensions of the Oldham Notebooks, Johnson and Elder write:

> …although no paper evidence has come to light, evidence from a filmed interview with Steptoe screened in 1980 (Williams, 1980) reveals that he asked for an assurance from all patients undergoing IVF and embryo transfer that they would permit an amniocentesis on any pregnancy and would agree to a termination if an abnormality was found. (Johnson and Elder 2015: 42)

Of course, this sort of caveat would never be allowed to happen now (at least not in a properly regulated setting). At the time, evidence also suggests that Steptoe and Edwards were highly aware of their work's experimental nature and were at least attempting to inform patients of the nature of the procedures. Again, Johnson and Elder (2015) provide evidence from the Oldham Notebooks of extracts of Steptoe's correspondence with prospective patients:

> "at present our work is highly experimental... and it is very difficult for us to forecast research work of this nature." (11 September 1970); "I must stress, however, that our work is highly experimental at the moment and it may be [sic] some time before we are in a position to offer help..." (13 November 1970); "We are still working to try and help people to have their own children and, although we are much closer to success than we were in 1968, there is still some way to go..." (26 January 1973); "Our work must still be considered exploratory..." (15 October

> 1975); "I must stress that our work is still experimental at present and we can make no promises..." (23 August 1976). (Johnson and Elder 2015: 42)

This is reinforced by evidence that has emerged of Steptoe and Edwards' success rate at IVF, which found that they (at least) undertook:

> …the application of 495 potential laparoscopic cycles to 282 patients to produce two live healthy babies, three lost established pregnancies, and perhaps 11 lost early pregnancies (although the evidence for most of these pregnancies is slim; Elder and Johnson, 2015a, 2015b, 2015c). (Johnson and Elder 2015: 42)

Furthermore, the UK Medical Research Council (MRC) declined to fund for their research, and this decision was heavily influenced by ethical concerns (Johnson and Elder 2015). Therefore, we need to reflect carefully before responding to safety concerns in debates about radical innovation by saying anything along the lines of: 'IVF was risky but we had to take a leap of faith and try that – what has changed? Why do we not just take a leap of faith with technology X?' Things have changed and need to continue changing. Altering the genetic constitution of future generations is moving into unknown territory. It remains hard to believe that in the context of radical innovation in assisted reproduction, it is still often up for debate about whether or not a radical innovation should be part of a research trial of any sort or if follow-up should be carried out on any offspring created. (For example, no follow up is being carried out on the first child created via mitochondrial replacement techniques – i.e., maternal spindle transfer) (Zhang et al. 2017).

The challenge of accounting for the costs of radical innovations is notoriously tricky. While costs in assisted reproductive medicine are typically framed in monetary terms, other significant costs should also be considered in these debates. For example, how much time and human resources will a procedure consume? Perhaps one of the most important but commonly overlooked questions is the following: what will the cost be to society's trust in science and science regulators? When He Jiankui announced in November 2018 that he had created two gene-edited offspring using IVF and CRISPR/Cas9, these revelations astonished the global medical, scientific, and ethics community (Cyranoski 2019). The consequence is that there have now been calls for a moratorium on human gene-editing, given the crisis of trust surrounding this technology's responsible use (Lander et al. 2019). Possibly, society's trust of regulators, the public, and the scientific community was already in a fragile state following the

2016 news that Dr. John Zhang created the first child using the mitochondrial replacement technique of maternal spindle transfer.

It could be argued that the recent events mentioned above have created a hostile environment for trust. If a radical innovation works and there is no harmful outcome, then perhaps it is a victory for society's trust in radical innovation in assisted reproduction. However, if something goes wrong – for example, offspring are created who live a life of suffering – then the harm to trust may be severe and hamper future progress in developing future assisted reproductive technologies. As we move toward a future that includes gene editing, in-vitro derived gametes, and ectogenesis, we need to consider what mechanisms could be put in place to cultivate and protect our trust in innovation. While we do not hesitate to innovate radical technologies that may affect future generations, regulators and ethicists often seem hesitant or disinterested in developing radical innovations to protect trust and patient safety. We owe it to future generations to radically innovate in regulation and ethics on a level that matches the level of radical innovation we see in assisted reproduction.

Conclusion

In summary, this chapter has aimed to respond to the following question: what are some of the key ethical challenges presented by radical innovations in assisted reproduction and, when possible, how should they be addressed? My response to this question has attempted to take into account Article 16 (Protecting future generations) of the UNESCO Declaration on Bioethics and Human Rights, which states that ‘the impact of life sciences on future generations, including on their genetic constitution, should be given due regard’ (UNESCO 2005).

My response is presented in four parts. First, I provided some terminological clarifications. Second, I argued that the emergence of radical innovations in assisted reproduction requires that we take a more nuanced approach to use the word ''parent’. Third, I argued that radical innovations in assisted reproduction, such as in-vitro derived gametes, have disrupted our traditional concepts of 'genetic relatedness' and our perception of future offspring's genetic constitution. Fourth, I argued that society has a responsibility to ensure that the introduction of radical innovations is translated from bench to bedside to prioritize safety, and we should proceed with radical innovation in a way that aims to foster trust.

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