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BACKGROUND PAPER

Artificial Gametes

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Note
The author was commissioned by the Nuffield Council on Bioethics to write this paper in order to inform the Council's discussions about possible future work on this topic. The paper is intended to provide an overview of key clinical, ethical, social, legal and policy issues, but is not intended to offer any conclusions or recommendations regarding future policy and practice. Any views expressed in the paper are the author's own and not those of the Nuffield Council on Bioethics.

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Introduction

In 2003-4, several research groups published work on the derivation of gamete type cells from mouse embryonic stem cells (ESCs).[1,2,3] Further reports emerged in 2004-5, based on research on human ESCs.[4,5] Since these initial developments, researchers have continued to work on the creation of gametes, and their use in research and reproduction may become feasible in the future. It has been suggested that these developments could 'democratise reproduction',[6] and even 'end infertility'.[7] In this report, we show how the development of artificial gametes has progressed and discuss the motivations of these research endeavours, and the ethical issues that they raise. It is necessary to highlight the fact that much of this discussion is necessarily speculative. Artificial gametes are in the process of development and as with any other area of scientific research, it may be that there is a sudden breakthrough much earlier than anticipated. Alternatively, AGs may never come into use, for reasons that are not yet apparent to us. What *is* clear is that there is ongoing research, yielding incremental advances, and the development and use of AGs in human reproduction and research is deemed plausible by credible commentators, including for example the UK's Human Fertilisation and Embryology Authority, as we will discuss later on in the paper.

The creation of artificial gametes has been motivated in relation to two main ends: firstly, generating further knowledge, especially with a view to the development of stem cell medicine, but also for understanding and learning to counter the effects of infertility. Secondly, this research has been motivated by the aim of eventually generating gametes for use in reproduction.[8] Amongst research reports in this area, some emphasise the former aims and related benefits,[9,10,11,12,13] while others emphasise the latter[14,15].

A note on terminology

Early publications used the term 'synthetic gametes', and perhaps the most used commonly-used term for cells created in this way is 'artificial gametes'. These may however be misleading terms, as the gametes in question are not created *de novo* from inorganic matter, but by manipulating already existing cells. The terms 'synthetic' or 'artificial' gametes have fallen into disfavour with some commentators, with 'synthetic gametes' now largely abandoned. In 2014 the Journal of Medical Ethics ran a special issue on this topic, using the term 'stem cell-derived gametes', while the articles eventually published in the issue used a wide variety of terms (see http://jme.bmj.com/content/40/11.toc). For brevity, we use the term artificial gametes throughout this report, shortened to 'AGs'. We acknowledge the baggage that comes with this term, but note that there is no universally accepted alternative, and that such alternatives as there are may also come with implicit loading and be replaced in the near future.

Section 1: The current state of the art

Most cells in a human's body ('somatic' cells) contain two sets of 23 chromosomes, one inherited from the each parent. A cell on its way to becoming a mature gamete (a 'germ' cell) undergoes a process called meiosis. The chromosomes pair up, and some genetic material is exchanged between the matching pairs of chromosomes. It is this that ensures that each gamete will be genetically unique. The chromosome pairs then part, and the cell divides, separating the two shuffled sets of 23 chromosomes. The process repeats, resulting in four gamete cells now containing only 23 chromosomes. This means that the cell can now fuse with another gamete to generate the 46 chromosome blastocyst which will develop into the embryo.

Scientists are exploring several pathways in their quest to create gametes in vitro. Hendriks et al describe these pathways in detail in their systematic review, published in 2015. They identify 8 biologically plausible routes towards the production of artificial sperm in males, and 9 biologically plausible routes towards the production of artificial oocytes in females. Additionally, they identify 9 biologically plausible routes that could lead to the development of artificial oocytes in males and 9 biologically plausible routes that could lead to the development of artificial sperm in females.

According to Hendriks et al, clinical application is the expected outcome of this research. However, they note that the state of knowledge concerning functionality and safety of human AGs is still preliminary. Below we provide a very brief overview of the key methods currently

being used in the derivation of AGs. Except where specific additional references are given, the information below derives from the Hendriks paper.

1.1 Embryonic stem cells (ESCs)
When a newly fertilised egg has undergone a few stages of cell division, cells removed from the inner cell mass have the capacity to develop into any cell of the body. These are cells from which embryonic stem cell lines (ESCs lines) can be derived.[16,17] Much research is being focussed on ways of initiating and controlling the process of differentiation in embryonic stem cells, including their differentiation into gametes.[18] Sperm from males and eggs from females have been derived using these techniques, in both animal and human models, with fertilisation and offspring reported in animals, but not humans. Furthermore, eggs have been derived from male mouse cells using this technique, and fertilised with artificial sperm from the same male mouse source.

1.2 Germline stem cells (GSCs)
Germline stem cells exist within reproductive tissue in the testes or ovaries. Unlike ESCs, their potential to develop into other types of cell is limited: they can *only* become reproductive cells. The tissue containing GSCs can be removed from the body and cultivated in conditions that enable them to generate functional gametes in the laboratory.[19] Egg cells have been derived in animal and human models, and have been successfully fertilised in mice. Sperm cells have been derived in mice, with birth of viable offspring reported. Female human GSCs have been transplanted into mice, resulting in artificial human eggs.

1.3 Haploidisation
When a somatic cell is injected into an egg cell which has had its nucleus removed, it may undergo the process of meiosis as described above, leading to the formation of a gamete despite the cell's somatic origins..[20,21,22,23] Human eggs formed in this way have been fertilised using ICSI.

1.4 Induced pluripotent stem cells (iPSCs)
iPSCs are created by reprogramming ordinary adult somatic cells to induce pluripotentiality.[24] Once iPSCs have been created, the derivation of gametes can follow the same path as that involved in ESC gamete derivation. Artificial oocytes have been derived from mouse cells using this technique. One of the achievements reported following the use of iPSCs is the creation of fertile mouse offspring from ooctyes derived from skin cells[25]. Artificial sperm has been obtained from female human cells using this technique.

Section 2: Artificial gametes in research

2.1 Learning from AGs
Since we do not yet have in vitro models of male or female gamete development, there is much still unknown about the development of human gametes. The ability to generate and study AGs in vitro is expected to increase knowledge in this area. In turn it is hoped that this will boost understanding of pathologies which particularly affect the germ cells, and allow researchers to learn more about the causes of infertility.[26]

Commentators responding to early developments in AGs research also believed that they could lead to an improved understanding of the processes involved in genomic imprinting.[27,28] It is well known that gene expression differs depending on whether a particular chromosome was inherited from the mother or from the father.[29] Some sources of AGs exemplify imprinting anomalies, which may shed light on the conditions that affect imprinting, leading to greater control.

2.2 Germ line engineering

It has been speculated that AGs could have an impact on research into new targeted opportunities for genetic interventions. Rick Weiss writing for the Washington Post in 2003 suggested that the development of AGs 'opens the door to creating 'designer' eggs from scratch',[30] while Smith, Chan and Harris identify AGs as a potential route for effective gene manipulation.[31] Robert Sparrow suggests that being able to undertake germ line engineering with gametes in vitro would enable scientists to work through multiple generations of embryos in a relatively short space of time. This, he argues, could offer a way of 'breeding out' certain genetic diseases or breeding in desirable genetic traits, which could then be passed on to future generations.[32]

Section 3: Ethical aspects of human AGs in research

3.1 Creation, manipulation and destruction of embryos for research

Any uses of AGs that involve the destruction of human embryos are likely to be regarded as unethical by those who object to embryo research. However, it might be that some people would perceive embryos created with AGs as having a different moral status from other embryos.[33] Newman and Lippman use the term 'assemblages' to describe organisms created from the fertilisation of AGs, implying that they are not obviously of equal moral status with 'real embryos'.[34]

If children born from AGs would share the same moral status as any other children — and the suggested use of AGs for reproductive purposes implies that they would — it is hard to see why it should be morally preferable to perform research on the embryos which could become such children, than to perform research on any other embryos. Newman and Lippman's point is not so much that AG embryos would or should have a different moral status from other embryos, but that the ability to create AG embryos would exacerbate the commodification of embryos that they already perceive to be a problem.

3.2 Overcoming the egg shortage in human stem cell research

In the early days of embryonic stem cell research, extravagant claims were made about the potential of such research to generate solutions to a wide range of human ills. However, the pace of achievements in this area has been relatively slow, partly as a result of difficulties in obtaining the necessary materials, especially human eggs. The proportion of embryonic stem

cell lines developed to eggs used is low.[i] Consequently the need for eggs in this area of research has not diminished, and seems unlikely to do so unless there is a major breakthrough in iPSC technology, which does not rely on human eggs.[35]

Egg harvesting is invasive and can be risky. There is a tension between the interests of researchers in obtaining eggs, and the interests of donors, especially where there are gender and power imbalances.[ii] These issues were highlighted in the debacle surrounding the work of Woo Suk Hwang in Korea. Initially, it was reported that Hwang had used 242 donor eggs in his attempts to create a single stem cell line.[36] Subsequently it emerged that over 2000 eggs had been used, while none of his stem cell lines could be verified.[37] Moreover, eggs used for Hwang's research had been obtained from female employees, for whom egg donation was treated as a part of their contractual obligations, in defiance of standard ethical guidelines.

Generating oocytes in particular in the laboratory might mean that the ethical and practical challenges of egg procurement would no longer be a problem.

3.3 Germline modifications and eugenics

As Sparrow notes, AGs could facilitate genetic modification of gametes that would be inherited by future generations. The prospect of research into germline modifications and genetic engineering raises many of the same issues that apply to eugenics more broadly. For more detail on the ethical debate surrounding eugenics, we recommend the booklet by Wilkinson and Garrard, which outlines the key ethical perspectives.[38] Wilkinson and Garrard's approach is cautiously permissive; however they note that there are people who object to anything that could be described as eugenic even if it might not directly harm offspring.[39]

Section 4: Regulatory challenges posed by the use of AGs in research

4.1 Loosening regulatory control

The Warnock Report's insistence that embryos should not be used 'frivolously' and that each embryo has a special moral status, relied at least in part on the idea that embryos for use in research are not easy to obtain. Scientists currently depend either on embryos donated by people who have given explicit consent for their use in research, or on specially created embryos, for which licences have to be obtained. Embryos from either source have to be used in ways that meet the terms of the licences obtained for them. Each individual embryo can thus be construed as an individual regulatory entity whose existence and destiny is known to, and governed by, the regulators. However, when scientists can create gametes in vitro it will be more difficult for regulators to exercise tight control over every single embryo used in research. This is not just because researchers may be able to create embryos with materials they already legitimately hold, but may also relate to the fact that embryos created with AGs

[i] A paper published in 2013 did report the derivation of stem cell lines using only 2 oocytes but this is not, to our knowledge, something that has been replicated on a wide scale. Tachibana M, et al. Human embryonic stem cells derived by somatic cell nuclear transfer. Cell 153.6 (2013): 1228-1238.

[ii] For a discussion of this, see for example: https://www.york.ac.uk/res/sci/events/ParryDonatingEggsEvent.pdf.

may be different from other embryos. Some AGs have given rise to parthenogenetic embryos; others to embryos whose genetic make-up is anomalous. Questions have already been raised concerning the way that the law interprets the meaning of 'embryo'[40] and indeed, of 'gamete' in the UK, leading to new legislation that attempted to be more specific.[41]

4.2 Reproductive potential as a disincentive to donation for research

Most embryos used in research are obtained from IVF patients. Theoretically, such patients could donate their embryos to other infertile couples instead. However, researchers have found that donors wish to avoid any prospect that offspring with their genes may be born in circumstances beyond their control.[42]

The idea that stem cell lines have the capacity for 'immortality' has added to the excitement with which stem cell research is regarded, and this has been picked up in the media and by bioethicists.[43,44] But the fact that a stem cell line can preserve a particular genetic lineage indefinitely may be worrying for potential donors, especially in view of the fact that sperm and eggs may be generated from it. As the public grows aware of the possibility that AGs can be developed from embryonic stem cells, concerns over control of one's reproductive potential might extend to embryos donated for research as well as those given for use in reproduction by other couples.[45,46]

It might be possible to allay such concerns by permitting donors to stipulate that their embryos would not be used for the development of AGs, or that any AGs produced would not find their way into reproductive medicine. However, ironically, this would also have implications in terms of limiting scientists' abilities to make advances towards the development of AGs.

Section 5: Possible uses of AGs in fertility treatments

In this section, we discuss the ways in which AGs might be used for reproductive purposes, and the implications that this might have for prospective patients, researchers, offspring, and society more generally.

5.1 Increasing supplies for sperm and egg banks

News reports suggest that sperm and eggs are in short supply in many clinics in the UK[47,48,49] and elsewhere.[50,51] The ability to create and proliferate AGs in vitro would increase the availability of gametes for clinics and gamete banks. There would, of course, be costs involved in meeting a shortfall in donor gametes through the production of AGs. However, mass production of AGs might bring these costs down.

5.2 Creating 'genetically related' gametes for the infertile

It is widely accepted that most people who use donated gametes would rather have their 'own' genetic child. Zsolt Nagy, previously a member of the team which developed the ICSI procedure, and his co-author, claim that '…patients with absent gametes or gonads represent the final frontier for infertility treatment'.[52] AGs could remedy this in ways that donor gametes would not, if for example, eggs or sperm could be 'made to order' from the cells of the patient seeking treatment. As with other potential uses of AGs, it is not possible to say with certainty when genetically-matching AGs may become available. Moreover, even once it becomes possible to create them, there may be safety and regulatory restrictions that lengthen the

interval between their development and their actual availability. Nevertheless, it is clear from much of the literature that the creation of genetically-matching gametes for use in fertility treatment is one of the expected end-point of research into AGs.

Researchers, however, are generally reluctant to be specific about time-frames, sticking to more cautious discussion of incremental advances.[53] In 2009, the HFEA's Scientific and Clinical Advances Advisory Committee (SCAAC) estimated that 'while research teams could produce sperm from stem cells by in (sic) the next few years, the production of eggs from stem cells could be longer. The group thought that it would be at least 5-10 years before eggs or sperm could be produced that could potentially be used in treatment.'[54] Similarly, in their 2008 'Consensus Statement: Science, Ethics and Policy Challenges of Pluripotent Stem Cell-Derived Gametes', the Hinxton Group (a group of scientists and other experts, constituted at the initiative of the Stem Cell Policy and Ethics Program (SCOPE) and the John Hopkins Berman Institute of Bioethics) state that 'the derivation of human eggs and sperm in vitro from PSCs, in whole or at least in part, is anticipated within 5 to 15 years'.[55] A group of researchers writing in Biology of Reproduction in 2012 discuss the many challenges and safety questions related to AGs, but conclude '... it is highly likely that AGs will represent powerful biological tools for reproductive science, a valuable training resource for embryologists and for potential use in the clinical treatment of human infertility.'[56]

5.3 Fertility for everyone

Testa and Harris refer to AGs as 'democratising reproduction',[57] while others have suggested that AGs will 'end infertility'.[58] This is because AGs might enable anyone to produce gametes regardless of whether they ever had 'natural' gametes, and irrespective of their age, sex, relationship status, or sexuality. The prospect of creating sperm from women's cells and eggs from men's cells might also democratise reproduction in enabling same sex couples to have children that are the offspring of both partners, something which has never before been feasible. Thus AGs offer the possibility of genetic reproduction to people who are not typically regarded as being infertile.

Current definitions of infertility, in use both in regulative documents and in fertility treatment, even when they are termed 'clinical', tend to describe a failure to achieve a particular end (production offspring) – rather than a physical status (e.g. lack of ovaries, azoospermia, etc.). For example, according to the World Health Organisation:

> *Infertility (clinical definition): a disease of the reproductive system defined by failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse.*[59]

This definition, although called *clinical* describes a lack of an expected outcome (success in reproduction) in certain circumstances. Lack of reproductive function will not qualify for infertility status, unless these other conditions are fulfilled (unprotected vaginal sexual intercourse). Same-sex couples might seem infertile according to this definition but in practice their infertility status will depend on legal interpretations in their legislature: whether or not same-sex couples are excluded from fertility treatments. Terminological choices and access

criteria to fertility treatments thus determine whether an individual or a couple who wish to avail themselves of such treatments can even be recognised as infertile and therefore eligible, for reasons that have more to do with (the nature of) their sexual activity and relationship choices, than with their actual capacity to reproduce.

We discuss the possibilities for specific groups of 'non-infertile' people below, along with brief outlines of the ethical issues raised by specific instances. Broader ethical concerns, such as harm to offspring, are discussed in the next section.

5.3.1 Same sex couples

If findings in mice are replicated in humans, egg cells could be obtained from human male somatic cell.[60] Eggs obtained from a man's somatic cell could then be fertilised with sperm from his partner, giving rise to children that are the genetic offspring of both.[61] Two women could also in theory have offspring together if the 'natural' egg of one woman could be injected with a haploidised cell obtained from the other.[62] Assuming the women have the usual XX chromosome complement, any child born would invariably be female, as there would be no Y-chromosomes involved.

Many jurisdictions now permit same sex couples to adopt children, and/or to undergo ARTs, and to be registered as legal parents. However, these developments are not universal; clearly in those jurisdictions where homosexuality is illegal, or where the rights of same sex couples are limited, same sex reproduction is not likely to be welcomed.

5.3.2 Solo parenthood

AGs could enable an individual to produce offspring without third party involvement, e.g. using AGs derived from her own somatic cells, to fertilise her 'natural' eggs.[63] Some commentators regard AG solo parenthood as particularly risky. Most individuals carry numerous mutated genes inherited from one or other parent, but which are 'neutralised' by a healthy copy inherited from the other parent. The risks to the offspring of solo AG reproducers would be similar to those involved if identical twins were able to reproduce together. Whittaker states that this must be legislated against at all costs.[64]

5.3.3 Postmenopausal parenthood

AGs could enable women to produce eggs after having gone through the menopause.[65] This would be likely to raise many of the same objections that have been levelled against 'social' egg freezing, postponement of parenthood and provision of treatment with donated eggs for postmenopausal women. For example, there are arguments that women using such techniques do not have a genuine need for treatment, that they should have reproduced at the optimal biological time rather than postponing motherhood.[66,67] However, AGs could mitigate some objections to postmenopausal motherhood: in a sense reproduction AG postmenopausal reproduction would become more 'natural' if eggs obtained from the women's own cells were used, allowing them to become the legal, birth and genetic mothers of their children. At the same time, this would be achieved through a process (the creation and use of eggs from their own somatic cells) much more technologically complex than it currently is (egg donation).

5.3.4 Pre-pubescent reproduction

AGs could also be used for pre-pubescent children, for example if they were undergoing medical treatment which might render them sterile.[68] As an increasing number of children survive cancer, this is becoming a more pressing issue. Currently, taking measures to preserve children's fertility before cancer treatment is controversial – and is in any case not always successful.[69] AGs could circumvent these problems.

Section 6: Harms and benefits arising from the use of AGs in reproduction

Above, we outlined ethical concerns related from the specific uses of AGs by individuals, same sex couples etc. In this section, we consider from a broader perspective what harms and benefits might accrue from the use of AGs in reproduction.

6.1 Relief of suffering caused by involuntary childlessness

From the earliest stages of research, AGs were discussed as a prospective treatment for infertility.[70] Because of the distress that infertility causes, as well as the high importance that reproduction is given socially, ethically and legally in many societies, anything that can help people to have a child might be seen to be ethically desirable. There are, of course, critics of ARTs, and to the extent that AGs are incorporated into the spectrum of available treatments, they will be subject to the same critique.

AGs may enable more people to have offspring genetically related to them, but their development will reopen questions about the degree to which people are *nudged* towards considering such technologies. Some feminists have argued against IVF and other ARTs on the grounds that they entrench the idea that women's sole or most important function is to become mothers.[71,72] A number of commentators in the field of reproductive ethics have questioned the great significance with which prospective parents, fertility doctors, and society at large, invest genetic connections in particular.

The development of AGs could place further pressure on women – and men – to pursue every possible avenue for genetic transmission.[73] Some representatives of fertility patients' organisations have already voiced such concerns.[74] This an issue that could apply to many new developments in ART; however the appeal of AGs does tend to be very specifically located in their potential to enable *genetic* transmission (as opposed to *gestating* a child, e.g. through surgical unblocking of fallopian tubes; reversal of sterilisation; womb transplants). AGs are likely to feed into understandings of reproduction that privilege genetic transmission. Here the technology would be put in the wider context of the right to reproduce / parent[iii] and what these can legitimately entail, and of natural as well as other means of assisted reproduction and the way policy unfolds (or should unfold) around them.

[iii] There is not scope for an analysis of reproductive or parenting rights here. However, for discussion see Deech R, and Smajdor A. From IVF to immortality: controversy in the era of reproductive technology. OUP 2007. Chapter 5. For discussion of parenting rights specifically, a useful source is Gheaus A. The Right to Parent One's Biological Baby*. Journal of Political Philosophy. 2012; 20.4: 432-455.

6.2 Harm to offspring

Children conceived with AGs might suffer serious genetic anomalies and this is a reason to be cautious in using such techniques. Many jurisdictions have implemented restrictions on the use of AGs in reproduction. Even after comprehensive animal studies, there will be some uncertainty as to the implications of AGs for human beings.

6.2.1 Genetic/medical harm

Avoidance of harm to offspring is accepted by many as the key or only moral concern relating to ARTs. Emily Jackson states that the avoidance of harm is 'as uncontentious as basing the decision not to prescribe a particular medicine to pregnant women upon evidence of is propensity to cause birth defects'.[75] John Harris argues that avoiding risks to offspring is 'the one decent argument against cloning.'[76]

There will undoubtedly be some risks associated with AGs. The process by which gametes develop naturally is complex and only partially understood at present. It seems possible that AGs might transmit serious genetic abnormalities.[77,78] Zubin Master notes the possibility that such defects might be inherited by future generations and could thus accumulate in the gene pool.[79]

There are also concerns about imprinting.[80] Despite AGs' resemblance to functional gametes, the development of an embryo might be affected by imprinting errors which are not yet fully evident. Some researchers express reservations specifically about haploidisation in humans, arguing that ESCs are likely to be safer than haploidisation for the development of AGs.[81] But whichever approach is favoured, there will be risks and uncertainties involved.

AGs have never, so far as we know, been used to produce human offspring. Evaluating 'unknown unknowns'[82] with respect to new technologies is challenging since by definition, such risks are impossible to identify. Any experimental procedure is likely to carry unforeseen consequences. Recent reports have indicated that children conceived using ARTs may be at increased risk of a variety of medical problems. Likewise, it is possible that unpredictable consequences could result from attempts to reproduce using AGs.

In the case of AGs and many other ARTs, the procedure itself is the means of creating the child. Those who believe that existence is in itself a benefit may hold that the minimum harm threshold applies: children conceived through a risky technique are not harmed provided they have a minimally satisfactory quality of life.[83,84] Others argue that this approach is flawed and that being brought into existence can neither harm nor benefit offspring, meaning that the harm/benefit analysis is of limited usefulness in reproductive ethics.[85]

Further research may succeed in resolving some or all safety concerns related to AGs. However, the move from research into reproductive uses of AGs and their actual arrival in the clinic will necessarily involve some uncertainty.

6.2.2 Psychosocial harm

AGs pose a variety of threats to the integrity of the nuclear family. Interpretations of how or whether family structures can harm children are contentious and highly politicised. These questions have for the most part, been widely discussed in the literature, with relation to other ARTs. Insofar as AGs may pose further challenges, these may arise partly from the greater scale on which AGs may allow for people's reproductive aspirations to be fulfilled, both within and without the nuclear family form.

Palacios-González et al speculate that AGs would allow greater scope for parents to choose between large numbers of different embryos. Where one has very few embryos to choose from, (because of the invasiveness of gamete harvesting, especially eggs) hair or eye colour may be a low priority concern in comparison to ensuring that the embryos to be implanted are healthy. But where eggs are plentiful, more embryos can be created, in which case the possibility of choosing between many healthy embryos on the basis of minor parental preferences, is more feasible.[86] This might alter the dynamics of the parent/child relationship – arguably the child becomes more like a 'product' that matches the parents' specifications, rather than a 'gift'.[87]

An aspect of AGs that does raise some new(ish) challenges is the question of whether an embryo used for the derivation of AGs is in fact the 'parent' of the offspring.[88,89] In turn this raises issues about what it might mean, psychologically, for a child to know that her parent never lived, and was destroyed in the process of her own creation. Another challenge with regard to parenthood is identified by Palacios-González et al, who note that AGs might facilitate the contribution of many genetic 'parents' to a single child. For example, suppose two people provide gametes from which an embryo is derived, in order to generate ESCs. These ESCs are differentiated into eggs, which are fertilised with sperm derived from ESCs obtained from a different embryo. If the sperm and eggs obtained through this process are fertilised, the offspring will be genetically related to the four adult 'parents', and clearly, by continuing through the cycle, many more contributors would be able to participate.[90] Those who fear the effects of family confusion on offspring,[91] may regard this as a worrying prospect.

Furthermore, the derivation of eggs from male cells and sperm from female may raise concern over the pressure that this adds to the already strained concepts of mother, father, and family. This new development would arguably make it even more challenging for legislatures to handle decision-making in these areas: for example, what will be the legal relation between a man and the child conceived using his eggs, or that between a woman and the child conceived using her sperm? Previous legislative endeavours have had struggled to defining these novel relationships, see e.g. in the UK the birth mother and her same-sex partner who can be the child's *other parent*: and not the child's other mother. If until now every child has had a genetic mother and a genetic father, even this basic statement could be challenged.

Section 7: Regulatory challenges related to the use of AGs in reproduction

One challenging question for researchers working on AGs for use in reproduction is that of safety. New procedures sometimes find their way into clinics without necessarily having undergone the kind of rigorous research process testing that would be essential for a new pharmaceutical intervention, for example. ICSI is one example of this, as is, arguably, IVF itself. Attempts have been made to tighten things up, hence the specific term in UK law of 'permitted' gametes, which was introduced specifically to distinguish between AGs and 'real' gametes. Currently AGs are not classed as 'permitted' gametes. However, as with other innovations in reproductive technology – most notably perhaps the UK's decision to allow mitochondrial transfer – this will not present an insurmountable hurdle, though it is likely to involve further legislation and public debate.

Aside from the legislative and regulatory challenges of moving from bench to clinic, AGs have the capacity to pose a fundamental challenge to many assumptions about the limits of human reproduction. These will also have an effect on legislation and regulation. Old age, prepubescence, lack of ovaries or testes, or loss of fertility resulting from cancer treatment will no longer spell a lack of reproductive capacity. In theory, it may be possible for any individual to produce gametes and thus to produce offspring (which is what Testa and Harris mean by the 'democratisation' of reproduction). However, this breadth of scope poses challenges for regulators. This is perhaps the most significant issue arising from the development of AGs.

Some of the innovations in human reproduction that might be actualised by the use of AGs in human reproduction may be no more challenging for the legislators than other recent situations such as the recognition of same-sex parents, of transwomen giving birth, or of parental status for more than two adults per child. One possible solution to this is for legislators to let go of the expectation that each child has two parents, one mother (preferably who contributed eggs) and one father (preferably who contributed sperm), and generally to revise the legal framework based on different criteria: one such revised expectation could rely on empirical research on different family forms, that quite consistently indicates that what matters most for children's wellbeing is family functioning (the quality of relationships within the family), regardless of genetic connections, family form, number, gender, or sexual orientation of the parents.[92] Should legislators choose to focus on family functioning instead, then, intricacies such as those mentioned above (e.g. male genetic mothers or series of in vitro generations) would lose a lot of their weight.

7.1 Gamete theft

A more tricky regulatory challenge is the prospect of unwitting parenthood.[93] AGs will open the possibility of taking a person's cells and converting them to AGs for use in reproduction. Clearly access to biological material such as skin cells is much easier than access to a person's gametes, meaning that genetic reproduction without one's knowledge or consent becomes feasible. Legal and social provisions for parenthood are heavily reliant on biological and genetic facts in many jurisdictions and are similarly dependent on the assumption that such material cannot be obtained easily or without the originator's consent. Thinking about the

possibility of unwitting parenthood through AGs may help to analyse the connections between genes, parenthood and financial responsibility.

7.2 Funding issues

AG creation is likely to be complex and costly. To date, many of the sperm-type cells that have been derived were injected into the eggs that were fertilised,[94] suggesting that independent fertilisation was not possible. This is something which could be significant were the process to be applied to human fertility treatments on a large scale. In turn, this will have a bearing on the ability of health services and insurers to provide access to treatment – where these cover fertility treatment; or to be restricted to a selected very few fertility patients capable to afford them – where fertility treatment costs are not supported from health services and insurers.

In jurisdictions where fertility treatment is state-funded, AGs may pose a problem as the pool of claimants will plausibly be drastically increased. The expense of AG treatment will be exacerbated by problems in setting coherent inclusion and exclusion criteria for eligible patients, as we discuss below. Healthcare providers may find it simpler and cheaper to withhold AG treatment and leave it for the private market.

7.3 Eligibility for treatment

The development of AGs is likely to put pressure on existing access and eligibility criteria for fertility treatments. Regulatory problems have already emerged in relation to IVF and other fertility treatments in various European countries and beyond. AGs extend the scope of such controversies and increase the need to define more accurately and coherently how fertility treatments relate to reproductive need, if at all.[95]

For example, in line with the the World Health Organisation definition of infertility cited above, a single woman who lacks eggs is not infertile unless she has had unprotected sexual intercourse during the last 12 months or more. Implicit in this definition is the fact that the intercourse is supposed to be heterosexual, thus excluding same-sex couples – and this condition is made explicit in a number of legislatures such as in France[96] and Italy[97].

The development of AGs will challenge our definitions of (in)fertility: if somatic cells in my body can also generate viable embryos, then if I do not have viable eggs, am I any less fertile than a woman who has viable eggs but does not seem able to reproduce *naturally*?

In the context of IVF, we have seen controversy and dispute about access for same sex couples or single claimants. Since AGs ‘democratise reproduction’, these disputes are likely to become more pressing, as people who currently have no prospect of genetic transmission (e.g. postmenopausal women) might feel encouraged to pursue reproduction.[98] Because of this, AGs may increase rather than decrease the suffering caused by infertility, if patients are aware that remedies exist, but they are unable to access them.

Conclusion

The pathways towards AGs that scientists are currently exploring include derivation of AGs from embryonic stem cells, from germline stem cells, via haploidisation, and from induced pluripotent stem cells. This research is motivated with reference to either scientific aims (growth of knowledge, provision of research material less controversial than donated gametes) or reproductive aims (contribution to treating infertility, or direct use in reproduction). AGs are said to have the potential to contribute to expedited stem cell research; to germline engineering; overcoming gamete shortage in research and treatment; to helping prospective parents have genetically related children; and in general 'democratise reproduction'. Ethical concerns in this area have included the commodification of human reproductive material; the question of whether funding for this research is warranted at all; a loosening of regulatory control; genetic or psychosocial harm to offspring; gender and parenthood issues; and risks that without a reconsideration of claims to treatment and infertility status, the use of AGs in reproduction would at the same time make it possible for the first time for certain categories of people to become genetic parents and be excluded depending on how access criteria and infertility status are defined.

Thus, the prospect of the use of AGs in research, treatment for degenerative diseases, and fertility treatment raises some familiar and some new ethical concerns. Even before it reaches a stage where AGs can be used in human reproduction, the technology is here and holds promise much beyond this particular application that has attracted most media attention. This is why the ethical discussion is not rendered obsolete by dismissing the direct use in reproduction. Furthermore, the possibilities that these technologies have raised already contribute to a need to further refine or altogether redefine established definitions such as that of infertility, of what a gamete is, or of what it is to be a genetic parent.

In short, some of the questions that the development and prospective uses of AGs raise are:

- What are the justifications of investing resources in work towards the development of AGs?
- Should it become possible that AGs are used directly in human reproduction, what degree of risk is acceptable and how can these risks be assessed in advance?
- Should the degree of risk be deemed acceptable, how should access criteria to fertility treatments be altered to incorporate the new possibilities?
- Should current definitions of infertility be revised in the light of the possibilities raised by research towards the development of AGs, and if so, how?
- Should more be done to question the attachment to the genetic link between parents and children that motivates at least some of the research efforts as well as monopolises most of the public attention to research towards developing AGs?

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