Received: 15 January 2018 | Revised: 6 June 2018 | Accepted: 28 June 2018

DOI: 10.1111/bioe.12505

ORIGINAL ARTICLE

WILEY bioethics

In vitro gametogenesis and reproductive cloning: Can we allow one while banning the other?

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Funding information
Instituut voor Innovatie door Wetenschap en Technologie, Grant/Award Number: 150042

Abstract

In vitro gametogenesis (IVG) is believed to be the next big breakthrough in reproductive medicine. The prima facie acceptance of this possible future technology is notable when compared to the general prohibition on human reproductive cloning. After all, if safety is the main reason for not allowing reproductive cloning, one might expect a similar conclusion for the reproductive application of IVG, since both technologies hold considerable and comparable risks. However, safety concerns may be overcome, and are presumably not the sole reason why cloning is being condemned. We therefore assess the non-safety arguments against reproductive cloning, yet most of these can also be held against IVG. The few arguments that cannot be used against IVG are defective. We conclude from this that it will be hard to defend a ban on reproductive cloning while accepting the reproductive use of IVG.

KEYWORDS
assisted reproduction, in vitro, gametogenesis, genetic relatedness, reproductive cloning, reproductive ethics

1 | INTRODUCTION

Both the creation of stem cell-derived (SCD) gametes by means of in vitro gametogenesis (IVG) and reproductive cloning could enable certain categories of (medically or socially) infertile couples to reproduce without the involvement of a third-party gamete donor. However, while IVG is met with careful enthusiasm in the scientific community, reproductive cloning is met with moratoria and bans. In this paper we explore the moral arguments that are employed to oppose the use of reproductive cloning in case of involuntary childlessness, and inquire if or how these arguments also hold for the reproductive use of SCD gametes obtained from a person's reprogrammed somatic cell.[1]

We first introduce both applications and discuss how arguments based on safety concerns can be held against both reproductive cloning and IVG.[2] If one recognizes that both technologies hold similar safety risks, and if one believes that reproductive cloning should not be pursued because of these risks, it could be argued that one should conclude the same for the reproductive use of person-specific SCD gametes. Safety-based arguments may, however, not be the decisive or exclusive concern. In the next section, we express our doubts about whether the benefits of IVG are able to outweigh the

[1]We will refer to this as person-specific SCD gametes (see below).

[2]We will not consider the non-identity argument here, *viz.* the argument that offspring cannot be harmed by being brought into existence by a risky technique since without the use of it they would never have existed, provided that their level of welfare is not below the standard of wrongful life. For a discussion of this argument, see Lawlor, R. (2015). Questioning the significance of the non-identity problem in applied ethics. *Journal of Medical Ethics*, *41*, 893–896. Lawlor makes clear that the conclusion of the non-identity argument is not the consensus view within bioethics. Moreover, if one does adhere to the non-identity argument, it would dismiss safety concerns for both reproductive cloning and IVG. As we are looking for morally relevant differences between reproductive cloning and IVG (justifying a different approach), whether safety is considered relevant for both or irrelevant for both has no impact on our general conclusion.

risks, while the benefits of reproductive cloning are not. Yet, as these safety concerns are based upon the present state of the art, and as it is possible that the current risks might be overcome over time, we then assess whether non-safety-based arguments against reproductive cloning can justify a prohibition on reproductive cloning, but not on the reproductive use of person-specific SCD gametes. We conclude that, on the basis of these moral arguments, it will be hard to defend a ban on reproductive cloning while accepting the reproductive use of person-specific SCD gametes. It should be noted that we cannot discuss all possible moral arguments against reproductive cloning that have ever been formulated, so we only discuss those that have most significantly shaped (and continue to shape) the ethical debate about human cloning. We do not exclude that in the future other moral arguments could be advanced to conclude that reproductive cloning is morally wrong, without affecting the moral acceptability of IVG.

We also wish to point out that we will focus on reproductive cloning for infertility reasons (medical or social) and that we will not discuss other, somewhat dubious, motivations, such as cloning to create 'copies' of admired individuals, to bring deceased persons 'back to life', or to assemble an army of persons created by cloning. We assume that, above all, the demand for both technologies will come from medically or socially infertile people who want to conceive a child. In response, however, it could be argued that allowing cloning for infertility reasons might ultimately culminate in the use of cloning for these other purposes that are deemed (even more) controversial. Thus, it may be held that even if the moral arguments regarding both technologies are very similar, there may still be pragmatic reasons for legally banning reproductive cloning but not IVG.[3] Yet, if one were to accept these pragmatic reasons to legally ban reproductive cloning altogether, one would have to show why this same reasoning would not apply to IVG, since besides the use for infertility reasons, there are possible 'controversial applications' of IVG as well.[4]

2 | HUMAN REPRODUCTIVE CLONING AND REPRODUCTIVE USE OF SCD GAMETES

We here understand human reproductive cloning as the creation of a human being by means of somatic cell nuclear transfer (SCNT). SCNT involves the insertion of a somatic cell nucleus into an enucleated oocyte. This would result in the asexual production of an individual who would have the mitochondrial DNA (mtDNA) of the oocyte donor (which is about 0.15% of the future child's DNA), and shares the rest of his/her DNA with the donor of the somatic cell nucleus. Young women could use their own oocytes for this procedure so that there would be no 'foreign' mtDNA present in the resulting child.

Producing person-specific gametes by means of IVG requires either the creation of an embryo via SCNT and differentiation of the embryonic stem cells (ESCs) into gametes, or creation of induced pluripotent stem cells (iPSCs) and derivation of gametes from these.[5] For both routes a somatic cell would be used, of the person for whom SCD gametes would be produced. The SCD gamete could then be combined with the complementary gamete of the other partner, resulting in an equal genetic relatedness between the future child and each parent.

The creation of 'customized gametes' has been lauded as a pathway to genetic parenthood for those who cannot procreate in a 'natural' way and is met with reserved enthusiasm. What we mean by 'reserved enthusiasm' is that, although there are calls for ethical reflection on this new technology, it is also portrayed as the next big breakthrough in reproductive medicine. Although clinical application in humans is not around the corner yet, Hendriks et al. believe that these studies are 'progressing steadily towards possible future clinical application'.[6] Cohen et al. stated that IVG raises some 'vexing policy challenges', but that it is 'poised for future success in humans and promises new possibilities for the fields of reproductive and regenerative medicine'.[7] The Hinxton Group is sympathetic to the reproductive use of SCD gametes, but only if appropriate oversight structures are in place, and if early attempts are done 'within the context of carefully conducted clinical research that conforms to the highest ethical standards'.[8] In the U.K., the Human Fertilisation and Embryology Authority Horizon Scanning Panel expressed a similar view, maintaining that more research is required prior to potential clinical applications.[9] It should, however, be noted that under the amended Human Fertilisation and Embryology (HFE) Act 1990, the U.K. currently precludes SCD gametes, like reproductive cloning, from clinical application. Yet, interestingly, the public consultation that preceded the review of the HFE Act, contained a call by the U.K. government to allow 'Parliament more flexibility to allow the use of [SCD gametes] in future should it wish to do so'.[10] With respect to reproductive cloning, however, the document stated that '[t]he Government does not intend that the review of the HFE Act will open up those fundamental aspects of the legislation'.[11]

[3]We thank an anonymous *Bioethics* reviewer for pointing this out.

[4]For an overview of such 'controversial applications' of IVG, see: Segers, S., Pennings, G., & Mertes, H. (2017). Ethical reflections on stem cell-derived gametes. *Médecine de la Reproduction*, *19*, 298–306.

[5]Hendriks S., Dancet, E. A., van Pelt, A. M., Hamer, G., & Repping, S. (2015). Artificial gametes: A systematic review of biological progress towards clinical application. *Human Reproduction Update*, *21*, 285–296.

[6]Ibid., p. 286.

[7]Cohen, I. G., Daley, G. Q., & Adashi, E. Y. (2017). Disruptive reproductive technologies. *Science Translational Medicine*, *9*(372), pii: eaah5645.

[8]The Hinxton Group is an international and interdisciplinary group of mainly scientists, ethicists and lawyers that originally started as a project to review and debate ethical and legal challenges raised by stem cell science and embryo research. In 2009 they published their recommendations on the ethico-legal issues that would be raised by IVG. See: Mathews, D. J. H., Donovan, P. J., Harris, J., Lovell-Badge, R., Savulescu, J., & Faden, R. (2009). Pluripotent stem cell-derived gametes: Truth and (potential) consequences. *Cell Stem Cell*, *5*, 11–14.

[9]Human Fertilisation and Embryology Authority. (2010). *Scientific Horizon Scanning at the HFEA. Annual Report 2009/10*. London: Author.

[10]Department of Health. (2005). *Review of the Human Fertilisation and Embryology Act. A public consultation*. London: Author. Retrieved June 1, 2018, from https://webarchive.nationalarchives.gov.uk/20130124071619/https://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4117872.pdf

[11]Ibid., p. 7.

In most countries, reproductive cloning is not allowed and in many countries it can lead to custodial sentences.[12] On an international level, reproductive cloning is opposed by the United Nations and the Council of Europe.[13] It seems that the prospect of IVG in humans does not evoke a similarly dismissive public reaction. Although one could speculate that this might also have to do with an increased societal habituation to the influence of biotechnology on human lives, it may still be questioned why, apparently, this has not yet altered the consensus view on human reproductive cloning. Moreover, being (or not being) accustomed to certain practices does not, in itself, say how these should be valued morally.

3 | SAFETY

Moral arguments against human reproductive cloning very often point back to safety concerns.[14] There is, however, no clear-cut indication of the risks of this technology in humans. Apart from the failed attempt by Zavos and Illmensee to transfer a human SCNT embryo into a woman's uterus, no attempts of human reproductive cloning have been reported.[15] There is, nevertheless, ample experience with cloning in other species: Rodriguez-Osorio et al. report live offspring from 20 mammalian species created through SCNT.[16] Still, while various studies have reported on advancement of the SCNT protocols, and even though SCNT has entered commercial application in farm animals in several countries, the improvement remains marginal, and efficiency in terms of healthy offspring is still low.[17] Several studies show a range of developmental abnormalities in offspring created by cloning, as well as high losses throughout early pre-implantation, post-implantation, and pre- and post-natal development.[18] Inadequate reprogramming of the somatic cell nucleus is regarded as the main reason for this low efficiency and it is held that there is no scientific reason to expect that this would be any different in humans.[19] Thus, the general view is that overall cloning efficiency has not sufficiently increased to make the leap to human reproductive cloning.[20]

This raises the question whether creating person-specific SCD gametes would be that much safer. Like cloning, the creation of person-specific SCD gametes requires reprogramming of somatic cells. The success rate for reprogramming in humans is still very low, both for the SCNT and the iPSC route. It has been found that both ESC lines derived from SCNT embryos and iPSCs show a similar incidence of coding mutations, loss of imprinting and (epi)genetic defects, probably due to reprogramming as such, regardless of the reprogramming process.[21] It might be the case, however, that due to the epigenetic reprogramming that takes place upon fertilization through DNA demethylation, epigenetic defects could be corrected in the case of IVG.[22] If this would be so, then IVG would hold less risk of inducing epigenetic aberrations than cloning, as DNA demethylation seems to be the limiting factor in successful cloning.[23] It remains to be proven, however, whether this epigenetic remodelling could sufficiently reduce the risk of possible *de novo* epigenetic defects due to reprogramming. There are also concerns about increased risks for accumulation of chromosomal aneuploidies, with possible negative health impacts for the future offspring.[24] In view of this, it is believed that the risks are too high to use converted cells for therapeutic applications.[25] In addition, IVG will hold risks associated with the differentiation of these reprogrammed cells into gametes, especially regarding their chromosomal and epigenetic stability.[26] Moreover, the use of the SCD gametes in combination with other assisted reproductive

[12]In France, for instance, reproductive cloning is qualified as a 'crime against the human species' and punished by 30 years' imprisonment. See: United Nations Educational, Scientific and Cultural Organisation. (2009). *Report of IBC on human cloning and international governance*. Paris: Author. Retrieved May 25, 2018, from https://unesdoc.unesco.org/images/0018/001832/183235e.pdf

[13]Häyry, M. (2017). Synthetic biology and ethics: Past, present, and future. *Cambridge Quarterly of Healthcare Ethics*, *26*, 186–205; United Nations General Assembly. (2005). *International convention against the reproductive cloning of human beings. Report of the sixth committee*. New York, NY: Author. Retrieved May 31, 2018, from https://digitallibrary.un-.org/record/542699/files/A_59_516_Add.1-EN.pdf; Council of Europe. (1998). *Additional protocol to the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, on the Prohibition of Cloning Human Beings*. Strasbourg: Author. Retrieved December 20, 2017, from https://rm.coe.int/168007f2ca

[14]This is not to say, however, that there are no other ethical (non-safety based) arguments against reproductive cloning. These will be explored below.

[15]Zavos, P., & Illmensee, K. (2006). Possible therapy of male infertility by reproductive cloning: One cloned human 4-cell embryo. *Archives of Andrology*, *52*, 243–254.

[16]Rodriguez-Osorio, N., Urrego, R., Cibelli, J. B., Eilertsen, K., & Memili, E. (2012). Reprogramming mammalian somatic cells. *Theriogenology*, *78*, 1869–1886.

[17]Loi, P., Iuso, D., Czernik, M., & Ogura, A. (2016). A new, dynamic era for somatic cell nuclear transfer? *Trends in Biotechnology*, *34*, 791–797; Niemann, H., & Lucas-Hahn, A. (2012). Somatic cell nuclear transfer cloning: Practical applications and current legislation. *Reproduction in Domestic Animals*, *47*, 2–10; Keefer, C. L. (2015). Artificial cloning of domestic animals. *Proceedings of the National Academy of Sciences of the United States of America*, *112*, 8874–8878; Long, C. R., Westhusin, M. E., & Golding, M. C. (2014). Reshaping the transcriptional frontier: Epigenetics and somatic cell nuclear transfer. *Molecular Reproduction & Development*, *81*, 183–193.

[18]Ibid.; Dinnyes, A., Tian, X. C., & Oback, B. (2016). Nuclear transfer for cloning animals. In R. A. Meyers (Ed.), *Reviews in cell biology and molecular medicine* (pp. 79–117). Hoboken, NJ: Wiley-VCH Verlag GmbH & Co. KGaA; Wilmut, I., Bai, Y., & Taylor, J. (2015). Somatic cell nuclear transfer: Origins, the present position and future opportunities. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *370*(1680), 1–9.

[19]Rodriguez-Osorio et al., op. cit. note 16, p. 1871; Dinnyes et al., op. cit. note 18, pp. 106–107; Chung, Y., Matoba, S., Liu, Y., Eum, J. H., Lu, F., Jiang, W., … Zhang, Y. (2015). Histone demethylase expression enhances human somatic cell nuclear transfer efficiency and promotes derivation of pluripotent stem cells. *Cell Stem Cell*, *17*, 758–766.

[20]Dinnyes et al., op. cit. note 18, pp. 106–107; Jaenisch, R. (2004). Human cloning – The science and ethics of nuclear transplantation. *New England Journal of Medicine*, *351*, 2787–2791.

[21]Wilmut et al., op. cit. note 18, p. 7; Johannesson, B., Sagi, I., Gore, A., Paull, D., Yamada, M., Golan-Lev, T., … Egli, D. (2014). Comparable frequencies of coding mutations and loss of imprinting in human pluripotent cells derived by nuclear transfer and defined factors. *Cell Stem Cell*, 15, 634–642; Sebban, S., & Buganim, Y. (2016). Nuclear reprogramming by defined factors: Quantity versus quality. *Trends in Cellular Biology*, *26*, 65–75.

[22]Fraser, R., & Lin, C. (2016). Epigenetic reprogramming of the zygote in mice and men: On your marks, get set, go! *Reproduction*, *152*, R211–R222.

[23]Niemann, H. (2016). Epigenetic reprogramming in mammalian species after SCNT-based cloning. *Theriogenology*, *86*, 80–90.

[24]Moreno, I., Míguez-Forjan, J. M., & Simón, C. (2015). Artificial gametes from stem cells. *Clinical & Experimental Reproductive Medicine*, *42*, 33–44; Merkle, F., Ghosh, S., Kamitaki, N., Mitchell, J., Avior, Y., Mello, C., … Eggan, K. (2017). Human pluripotent stem cells recurrently acquire and expand dominant negative P53 mutations. *Nature*, *545*, 229–233.

[25]Sebban & Buganim, op. cit. note 21, p. 72.

[26]Hendriks et al., op. cit. note 5, p. 292.

technologies (ARTs), such as intracytoplasmic sperm injection, might lead to an accumulation of (epi)genetic mutations in the future offspring.[27] The creation of gametes from stem cells is also hindered by the fact that the risk of abnormalities increases with the time the cell lines are kept in culture.[28] Although the risks in IVG are more hypothetical than those in reproductive cloning (given the more extensive experience with reproductive cloning in other animals), it is fair to say that, at present, reproductive use of person-specific SCD gametes would be unacceptable given the high risks to the future child.[29]

4 | REPRODUCTIVE BENEFIT

As there is good reason to believe that IVG, like reproductive cloning, would hold considerable risks, a point could be made that if safety is the main reason not to proceed with human reproductive cloning, this would also hold for the reproductive use of person-specific SCD gametes. Accordingly, claims that further research might minimize the risks associated with IVG could also be applied to the case of reproductive cloning. Now, it may be countered that even if the risk of IVG is comparable to that of reproductive cloning, there may still be an additional reproductive benefit to IVG that could outweigh this risk. That is, IVG could allow couples to parent a child who shares approximately 50% of both parents' DNA. Reproductive cloning, on the other hand, only leads to genetic relatedness between the future child and one parent, with the exception of a minimal link to the mother if the female partner's oocyte is used to clone the male partner. Two questions emerge here. First, can the prospect of shared and equal genetic relatedness between both prospective parents and the future child be regarded as a benefit of IVG over reproductive cloning? Second, to the extent that this is indeed a benefit, would it be important enough to justify taking higher risks?

With regard to the first question, it may be argued that the presumed added value is only relevant from the perspective of *couples* who wish to parent a child: for singles who wish to have a child of their own, the force of this presumed additional benefit would be cancelled out. For them, reproductive cloning would provide a strong genetic link with just one parent, which would be a benefit, rather than a disadvantage if this individual would prefer to avoid that his/her child would share half of his/her nuclear DNA with a gamete donor.[30] While acknowledging this, the claim that for *couples* IVG has something to add that reproductive cloning has not, may still be valid. Moreover, it should be noted as an aside that IVG also holds perspectives of solo reproduction, namely if a 'natural' gamete could be combined with a derived gamete from the same individual. However, since we all carry potentially disease-causing mutations, this would hold an extremely high risk of bringing such disease causing heterozygous mutations to homozygosity in the resulting child.[31] As genome sequencing techniques become more effective, a more accurate picture of the average number of potentially disease-causing mutations per person will become possible, which would also yield a clearer view on the risks of solo IVG.[32] In the light of this, Whittaker stated that 'reproductive cloning of humans might begin to look pretty safe'.[33]

As a further qualification of the claim that, at least for couples, IVG would have an added benefit over reproductive cloning, it could be argued that shared and equal genetic parenthood need not be the most important benefit for those requesting a form of assisted reproduction that would establish a genetic link. We cannot settle this issue here, but as already suggested in the previous paragraph and as indicated by Mertes, it may be that genetic parenthood is not what would be most important for many couples, but rather the avoidance of interventions in the family by other 'parent-candidates'.[34] And that, indeed, is something that can be achieved not only through IVG, but also through reproductive cloning. Both techniques hold the reproductive benefit of avoiding potential interventions by other 'parent-candidates', but both techniques also hold considerable risks. But while this should again be acknowledged, it remains the case that for those couples who do put value on shared and equal genetic parenthood, the fact that this can be obtained through IVG but not through reproductive cloning, would count as a reproductive benefit.

This brings us to the second question: how much risk to future children should we allow as a price for which presumed reproductive benefits? Based on the 'high risk of serious harm' or 'reasonable welfare' principle set out by the European Society for Human Reproduction and Embryology, '[t]he fertility specialist should refuse to collaborate in the parental project of the would-be parents if he or she judges that there is a high risk of serious harm to the future child'.[35] In view of the

[27]Master, Z. (2006). Embryonic stem-cell gametes: The new frontier in human reproduction. *Human Reproduction*, *21*, 857–863.

[28]Lund, R., Närvä, E., & Lahesmaa, R. (2012). Genetic and epigenetic stability of human pluripotent stem cells. *Nature Review Genetics*, *13*, 732–744.

[29]Segers, S., Mertes, H., de Wert, G., Dondorp, W., & Pennings, G. (2017). Balancing ethical pros and cons of stem cell derived gametes. *Annals of Biomedical Engineering*, *45*, 1620–1632.

[30]Devolder, K. (2014). Were it physically safe, human reproductive cloning may be permissible. In A. Caplan & R. Arp (Eds.), *Contemporary debates in bioethics* (pp. 79–89). Malden, MA: Wiley-Blackwell.

[31]Xue, Y., Chen, Y., Ayub, Q., Huang, N., Ball, E. V., Mort, M., … 1000 Genomes Project Consortium. (2012). Deleterious- and disease-allele prevalence in healthy individuals: Insights from current predictions, mutation databases, and population-scale resequencing. *American Journal of Human Genetics*, *91*, 1022–1032.

[32]Ibid.

[33]Whittaker, P. (2007). Stem cells to gametes: How far should we go? *Human Fertility*, *10*, 1–5.

[34]Mertes, H. (2014). Gamete derivation from stem cells: Revisiting the concept of genetic parenthood. *Journal of Medical Ethics*, *40*, 744–747. Although empirical evidence is not sufficient to settle a normative matter, it is also interesting to indicate that research has shown that lesbian couples raising donor-conceived children consider the genetic link as a 'valuable extra' (and not as a necessary condition for equality), but regard the avoidance of third party involvement as more important. See: Raes, I., Van Parys, H., Provoost, V., Buysse, A., De Sutter, P., & Pennings, G. (2014). Parental (in)equality and the genetic link in lesbian families. *Journal of Reproduction & Infant Psychology*, *32*, 457–468.

[35]See: ESHRE Task Force on Ethics and Law. (2007). ESHRE Task Force on Ethics and Law 13: The welfare of the child in medically assisted reproduction. *Human Reproduction*, *22*, 2585–2588. In this document, the context of natural reproduction is also compared to that of ART, where the involvement (and moral responsibility) of the assisting physician and the circumstances in which the future child is brought to life are considered to be morally relevant. This is further discussed in: de Wert, G. (1998). The post-menopause: Playground for reproductive technology? Some ethical reflections. In J. Harris & S. Holm (Eds.), *The future of human reproduction* (pp. 221–237). New York, NY: Oxford University Press; Cutas, D., & Bortolotti, L. (2010). Natural versus assisted reproduction. *Studies in Ethics, Law & Technology*, *4*, 1–18.

current safety risks that were discussed in the previous section, both IVG and reproductive cloning currently do not meet the standard for clinical applications. But what if the risks of both technologies could be minimized to, say, the level of risks we accept for other ARTs? This will be the subject of the remainder of this paper.

5 | ADDITIONAL NON-SAFETY-BASED ARGUMENTS

The discussion in the previous sections is necessarily based upon the current state of the art of both technologies. Thus, while there are good safety reasons not to proceed with human reproductive cloning at present, there might come a time in which its safety and efficiency will reach an acceptable level.[36] The same goes for IVG.

Now, even if one would grant that the risks of both technologies could be minimized to this level, this would not in itself be a sufficient condition for them to be morally acceptable. In the case of reproductive cloning, many people would probably still condemn it, even if it would be sufficiently safe. The fact that preclinical research into reproductive cloning is being forestalled points in the direction that safety is not the sole reason to condemn cloning (as this is a major impediment to making it sufficiently safe for clinical application). Additional non-safety-based arguments have been targeted against reproductive cloning, which might justify a decision not to clone humans. Thus, if one wishes to maintain a prohibition of reproductive cloning, but not of the reproductive use of person-specific SCD gametes, much will depend on the force of these additional non-safety-based arguments against reproductive cloning, as well as on how these affect IVG. In discussing these ethical arguments, we will inquire whether there are morally relevant differences between IVG and reproductive cloning that could justify a different moral judgment vis-à-vis these technologies.

5.1 | Dignity, instrumentalization, uniqueness and autonomy

Arguments that reproductive cloning is wrong because it breaches human dignity are commonly troubled because they often neither specify what 'dignity' means, nor why or how human reproductive cloning would breach it at all, or at least any more than other ARTs, including IVG.[37] Is it wrong because it would instrumentalize the person created by cloning, or treat him/her as a mere means?[38] The desire of having a (genetically related) child is the basis for most planned pregnancies though. As such, using reproductive cloning to overcome unwanted childlessness would not be more instrumentalizing than using IVG or other ways to have children, which can be said to be prima facie acceptable as long as these children are valued in their own right.[39]

Related arguments that cloning would breach the future child's 'right to a unique identity' and/or his or her 'right to an open future', have been discussed and refuted by, for example, Tooley and Brock.[40] Already on a purely technical level, the two persons would not be genetically identical (given that they might have different mtDNA and that they would differ epigenetically). Moreover, our genetic make-up is merely one part of our identity. As such, we do not consider identical twins to have the same identity. Furthermore, as persons created by SCNT cloning would grow up in a different time and environment, the differences between them would be even greater than the differences between identical twin siblings. Therefore, even if a 'right to a unique identity' did exist, it would not be breached by cloning. Likewise, the argument that cloning would restrict the future possibilities of the person created by cloning (because the somatic cell donor would already have made the life choices that are still in the future of the person created by cloning), is rooted in a false belief in genetic determinism.[41]

It may, however, be speculated that the person created by cloning may nevertheless *feel* that her autonomy is constrained and/or that she is not a unique human being. Such feelings could cause psychological distress and negatively affect one's well-being.[42] This is also the basis of Levick's psychological argument that the person created by cloning might have difficulty in developing a unique personal identity.[43] While speculative, this concern is not unlikely.[44] The concern is that because of the age difference between the person who is cloned and the person who is created by cloning, the latter might suffer from feeling pressure to be like the person whose genetic material was cloned. Indeed, this specific worry pertains much less to the case of IVG and natural reproduction, although it must be noticed that this is merely a difference in degree, not in kind, as children of successful adults may experience a similar kind of pressure. Yet, we do not outlaw reproduction of NFL players because of the pressure on their potential children. Also, it is important to notice that the actual impetus of this type of argument comes from the potential psychological harm to the future child, which is *not* exclusive to reproductive cloning, but also pertains to IVG.[45] Watt, for

[36]Devolder, op. cit. note 30, p. 81.

[37]Häyry, M. (2003). Philosophical arguments for and against human reproductive cloning. *Bioethics*, *17*, 447–460.

[38]Ibid.; Kahn, A. (1997). Clone mammals… Clone man? *Nature*, *386*, 119; Tooley, M. (1998). The moral status of the cloning of humans. In J. M. Humber & R. F. Almeder (Eds.), *Human cloning* (pp. 65–101). Totowa, NJ: Humana Press.

[39]Devolder, op. cit. note 30, p. 84.

[40]Tooley, op. cit. note 38, pp. 84–85, 93–94; Brock, D. (2003). Cloning human beings: An assessment of the ethical issues pro and con. In T. L. Beauchamp & L. Walters (Eds.), *Contemporary issues in bioethics* (pp. 593–602). Belmont, CA: Thomson Wadsworth.

[41]Ibid.; Devolder, op. cit. note 30, p. 82.

[42]Ibid.

[43]Levick, S. E. (2014). Were it physically safe, human reproductive cloning would not be acceptable. In A. L. Caplan & R. Arp (Eds.), *Contemporary debates in bioethics* (pp. 89–97). Malden, MA: Wiley-Blackwell.

[44]Levick tries to substantiate this with evidence from the practice of psychiatry (especially identical twin cases). See: Ibid. In the debate with Levick, Devolder also agrees 'that for some clones it may be psychologically somewhat more difficult', which need not, however, entail a prohibition on cloning. Devolder, K. (2014). Reply to Levick. In A. L. Caplan & R. Arp (Eds.), *Contemporary debates in bioethics* (pp. 98–100). Malden, MA: Wiley-Blackwell.

[45]In the past similar claims have also been made regarding IVF (which turned out to be untrue). Master, op. cit. note 27, pp. 859–860.

instance, has argued that children born from ESC-derived gametes might feel 'cast adrift on the world' since the embryo/genetic progenitor/gamete donor never existed as a person and could not possibly be known by the resulting offspring.[46] Similarly, having knowledge that an embryo had to be intentionally destroyed for the resulting child to live might be a source of discomfort.[47] Again, much will depend on how these issues will be framed and explained. The same goes for the iPSC-route: saying that pluripotent stem cells were differentiated into a gamete and combined with another gamete, rather than that one is created out of a skin cell, could make quite a difference. The bottom line is that these considerations are not less speculative than those regarding reproductive cloning.

It could be countered, however, that it is more likely that psychological harm will ensue from cloning and/or that it would be more severe than that ensuing from IVG. Apart from how one could possibly substantiate this claim, it is dubious what the normative implication would be of this line of reasoning. For one thing, there is an important difference between the potential psychological harm from cloning and that ensuing from IVG: in the case of cloning, such harm would be premised on a false belief, i.e., the belief in genetic determinism. It can sensibly be asked what such harm arising from false beliefs normatively implies.[48] At least in this case, it does not in itself provide a sufficient reason to ban cloning, rather than to engage in serious educational campaigns to correct the false belief in genetic determinism.[49]

5.2 | Creating offspring with a particular genome

A second type of argument against human reproductive cloning has to do with the moral unease that this technology could be used to create a child with particular genetic traits or to create people with a 'favourable' genotype.[50] However, IVG might also be directed towards this end. First, if IVG could be used to create large numbers of gametes, these could be used to create many embryos, which could facilitate screening and selection in accordance with the future parents' preferences.[51] A second scenario is to create SCD gametes from several individuals with desirable genetic traits which could then be recombined to create embryos, which would again be used to create SCD gametes, and so on until one obtains the embryo with the desired traits.[52] While in these scenarios, as well as in the cloning scenario, the 'choice' of the future child's genetic traits would be limited to the initial genotype from which one starts, this could be overcome by a third scenario in which IVG would facilitate direct genome editing. That is, if it were possible to edit (e.g., via CRISPR/Cas9) stem cells that were obtained from a person's somatic cell and if these could be differentiated into gametes through IVG, then this might facilitate the creation of a child with specific genetic traits through direct genome editing. However, it is not a priori evident that it is morally wrong to choose which genetic information to pass along to the future child (regardless of the technique that is employed to do this).[53] Moreover, even though both IVG and reproductive cloning could be used to create children with a particular genome, these specific uses could be prevented through regulation. Note that also PGD can be used to select an embryo based on non-medical traits, but that regulations and guidelines are put in place to limit such use.[54]

5.3 | Opportunity costs and conflicting interests

Another set of non-safety-based arguments against human reproductive cloning has to do with justice concerns. The most common version, which is according to some 'the most plausible case' against human reproductive cloning, holds that cloning affronts the just distribution of scarce public resources.[55] The assumption of this argument is that healthcare interests that fall short of a certain standard outweigh the reproductive interest that could be served by an expensive reproductive technology like cloning.[56] However, if one follows this line of reasoning, one should be aware that it also cuts across the case of IVG for reproduction: IVG will, at least in the beginning, most likely be an expensive technology and state funding of IVG treatment would also take away healthcare budget that could have been spent on other purposes.[57] Thus, this is a clear line of argument against human reproductive cloning, but it is similar to, if not exactly alike, the one that can be advanced against IVG (and the one that Rulli advanced against mitochondrial replacement techniques).[58]

A possible variant of this argument holds that allowing reproductive cloning in humans would imply 'the avoidable neglect' of the

[46]Watt, H. (2014). Ancestor embryos: Embryonic gametes and genetic parenthood. *Journal of Medical Ethics*, *40*, 759–761.

[47]Relatedly: for those who oppose the intentional destruction of human embryos, the SCNT route for creating person-specific SCD gametes would be a greater moral wrong than reproductive cloning: the former inherently involves embryo destruction, while the latter does not. This, however, only holds for the SCNT variant of IVG, as embryo destruction is not an inherent aspect of the iPSC route.

[48]Tooley, op. cit. note 38, p. 94.

[49]Lewontin, R. (2001). *It ain't necessarily so: The dream of the human genome and other illusions*. New York: New York Review of Books.

[50]Steinbock, B. (2006). Reproductive cloning: Another look. *University of Chicago Legal Forum*, *2006*(1), 87–112; Thomas, C. (2017). Novel assisted reproductive technologies and procreative liberty: Examining in vitro gametogenesis relative to currently practiced assisted reproductive procedures and reproductive cloning. *Southern California Interdisciplinary Law Journal*, *26*, 623–648.

[51]Bourne, H., Douglas, T., & Savulescu, J. (2012). Procreative beneficence and in vitro gametogenesis. *Monash Bioethics Review*, *30*, 29–48.

[52]Sparrow termed this scenario 'in vitro *eugenics*' (emphasis added). Yet, it could be nuanced that this technique is not necessarily eugenic, but that it could also be applied to obtain certain non-disease related traits in the future child that are not aimed at creating 'better' children. Sparrow, R. (2014). In vitro eugenics. *Journal of Medical Ethics*, *40*, 725–731.

[53]Kamm, F. M. (2005). Is there a problem with enhancement? *American Journal of Bioethics*, *5*, 5–14.

[54]For an elaboration, see: Segers, S., Pennings, G., Dondorp, W., de Wert, G., & Mertes, H *In vitro* gametogenesis and the creation of 'designer babies'. *Cambridge Quarterly of Healthcare Ethics* (forthcoming).

[55]Gillon, R. (2003). Human reproductive cloning: A look at the arguments against it and a rejection of most of them. In T. L. Beauchamp & L. Walters (Eds.), *Contemporary issues in bioethics* (pp. 621–632). Belmont, CA: Thomson Wadsworth.

[56]For a critical discussion of this argument, see Williams, M. (2009). Resource expenditure not resource allocation: Response to McDougall on cloning and dignity. *Journal of Medical Ethics*, *35*, 330–334.

[57]Segers et al., op. cit. note 29.

[58]For the discussion of mitochondrial replacement techniques, see Rulli, T. (2016). What is the value of three-parent IVF? *Hastings Center Report*, *46*, 38–47.

interests of children that are up for adoption.[59] The underlying idea is that reproductive cloning would take away the primary motivation to adopt, which would result in the neglect of the interests of those children who need to be adopted. Again, difficulties to predict such long-term consequences aside, this concern applies equally well to other forms of ART that provide alternatives to adoption.[60] As noted by Strong:

> If cloning should be prohibited in an attempt to help children who would benefit from adoption, then to be consistent should not one also advocate the banning of donor insemination, ovum donation, controlled ovarian stimulation, and in vitro fertilization?[61]

One could also add IVG to this list.

5.4 | Strangeness and the 'basic structure of sexual reproduction'

Finally, much of the opposition against cloning probably has to do with emotive 'gut' reactions: it is perceived as strange, unnatural and/or as a way of 'playing God'. Even if these feelings would be accorded moral weight, it can be asked whether IVG would be less strange or more natural. One might state that IVG would restore the 'natural order' of a woman and a man with genetically related children, but mere reference to the 'natural order' does not entail the normative conclusion that this is how things ought to be (unless one adds the moral premise that things that are according to the natural order, are good). Still, it can be noted that IVG and other ARTs differ from cloning, in the sense that cloning deviates from the 'basic structure of sexual reproduction—the combination of genetic material from father and mother resulting in a genetically unique child', of which the outcome is unpredictable, and the child's genetic endowment 'uncontrolled and undesigned'.[62] As we already noted, it is untrue that the person created by cloning will be identical to the person who is cloned, and as such the 'outcome' of the former's personal development remains unpredictable. It is true that cloning departs—more than IVG—from the basic structure of sexual reproduction in the sense that it is a form of asexual reproduction, but it is unclear why this would be a fundamental moral problem. Moreover, it seems that this argument is quite easily invalidated by the reversal test: imagine a world in which *ceteris paribus* human reproduction would happen in an asexual manner, via cloning, instead of in a sexual way. Would we then persist that it would be better from a moral point of view to switch to an artificial way of reproduction where two genomes are randomly reshuffled? It would seem to us that this unpredictability would rather be deemed suboptimal and dangerous, not in the least in view of possible risks for autosomal recessive genetic conditions that are transmitted to the future child when both parents carry the recessive trait.[63]

6 | CONCLUDING REMARKS

We explored the safety concerns for both reproductive cloning and the reproductive use of person-specific SCD gametes, and found that there is good reason to believe that both technologies presently hold comparable risks. In view of this, it could be argued that if safety concerns are the prime reason not to proceed with reproductive cloning in humans, it might inform a similar conclusion for the reproductive use of person-specific SCD gametes. This could justify a moratorium on clinical applications of both IVG and reproductive cloning, but not a ban on preclinical research into these techniques. Safety, however, is presumably not the sole reason for which cloning is being condemned. We therefore also explored some of the most current non-safety objections against reproductive cloning. We indicated that most of these arguments can also be held against the reproductive use of person-specific SCD gametes, and that those arguments that do not hold for IVG are ill informed or based on ill-defined concepts. From this it could be argued that if those arguments against reproductive cloning that can also be held against IVG are considered to provide a strong enough case against human cloning, the same conclusion would seem to follow for IVG. Or, conversely, that if one finds them unconvincing as arguments against IVG, the case against reproductive cloning should also be deemed inconclusive if it is based on these same arguments. It seems that, when push comes to shove, it will be hard to defend, on the basis of these arguments, a ban on reproductive cloning while accepting the reproductive use of person-specific SCD gametes.

ACKNOWLEDGEMENTS

This study was funded by the Agency for Innovation by Science and Technology in Flanders (IWT) (project number: 150042).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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[59] Levy, N., & Lotz, M. (2005). Reproductive cloning and a (kind of) genetic fallacy. *Bioethics*, *19*, 232–250.

[60] Strong, C. (2008). Cloning and adoption: A reply to Levy and Lotz. *Bioethics*, *22*, 130–136.

[61] Ibid., p. 135.

[62] The President's Council on Bioethics. (2002). *Human cloning and human dignity: An ethical inquiry*. Washington, DC: Author, p. 10.

[63] Silver, L. (1997). *Remaking Eden: How genetic engineering and cloning will transform the American family*. New York, NY: Avon.

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How to cite this article: Segers S, Pennings G, Dondorp W, de Wert G, Mertes H. In vitro gametogenesis and reproductive cloning: Can we allow one while banning the other?. *Bioethics*. 2018;00:1–8. https://doi.org/10.1111/bioe.12505