Queering the genome: ethical challenges of epigenome editing in same-sex reproduction

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ABSTRACT

In this article, I explore the ethical dimensions of same-sex reproduction achieved through epigenome editing—an innovative and transformative technique. For the first time, I analyse the potential normativity of this disruptive approach for reproductive purposes, focusing on its implications for lesbian couples seeking genetically related offspring. Epigenome editing offers a compelling solution to the complex ethical challenges posed by traditional gene editing, as it sidesteps genome modifications and potential long-term genetic consequences. The focus of this article is to systematically analyse the bioethical issues related to the use of epigenome editing for same-sex reproduction. I critically assess the ethical acceptability of epigenome editing with reproductive purposes from multiple angles, considering harm perspectives, the comparison of ethical issues related to gene and epigenome editing, and feminist theories. This analysis reveals that epigenome editing emerges as an ethically acceptable means for lesbian couples to have genetically related children. Moreover, the experiments of a reproductive use of epigenome editing discussed in this article transcend bioethics, shedding light on the broader societal implications of same-sex reproduction. It challenges established notions of biological reproduction and prompts a reevaluation of how we define the human embryo, while poses some issues in the context of gender self-identification and family structures. In a world that increasingly values inclusivity and diversity, this article aims to reveal a progressive pathway for reproductive medicine and bioethics, as well as underscores the need for further philosophical research in this emerging and fertile domain.

INTRODUCTION

In order for reproduction to occur, whether through natural conception or assisted reproductive techniques (ART), the participation of opposite-sex cells—an egg and a sperm—is necessary. This mechanism, widely conserved throughout mammalian evolution,[1 2] enables opposite-sex human couples to have descendants genetically related to both partners. The requirement for an egg and a sperm poses a challenge for same-sex couples seeking to have biologically related children. ARTs can be employed to allow biological reproduction of one partner but without knowing who provided the gamete. For gay couples, a procedure involving in vitro fertilisation (IVF) of a third-party oocyte with pooled sperm from both partners is used.[3 4] A random sperm fertilises the egg, resulting in an embryo that develops without knowledge of the biological father. Of course, a simple and non-invasive genetic test can be conducted at the fetal or newborn stage to determine the biological parentage. Indeed, a surrogacy is required to carry on with the pregnancy. For lesbian couples, there is an alternative that involves both partners. One partner provides an oocyte to be fertilised by third-party sperm, while the other carries the resulting embryo during pregnancy.[5 6] A second option is the use of mitochondrial replacement therapies, in which the resulting embryo comes from an oocyte containing the mitochondrial DNA from a mother and the nuclear one from the other.[7–9] A third option could be mixed gestation, through an intrauterine device named INVOCELL,[10] a partner could gestate an embryo during the preimplantation phase and a second one could continue the pregnancy from implantation to birth. Naturally, in this last case, the newborn will contain genetic information solely from the partner who provided the egg and, in all cases, male genetic contribution is required.

The requirement for the involvement of two opposite-sex cells in embryo fertilisation, a fundamental process in humans and many other mammals is linked to the phenomenon of imprinting.[11 12] Genomic imprinting, identified as an epigenetic mechanism, entails the tagging of DNA sequences through a process known as methylation. This involves the addition of small molecules (CH_3-, methyl groups) to DNA to regulate their expression in a manner specific to either the maternal or paternal lineage.[13 14] Consequently, DNA sequences marked with these methyl groups become silenced, rendering them incapable of expression, despite being present in the genome. In practical terms, a maternally imprinted gene refers to a DNA region inherited from the mother that remains unexpressed due to the presence of these chemical modifications. While genetics primarily concerns the information encoded in DNA using A, T, G and C molecules, epigenetics represents another layer that involves molecules capable of controlling when, where and how genes are activated or deactivated.[15 16] It is crucial to note that genomic imprinting does not alter the DNA sequence itself but significantly influences the behaviour of genes.

The potential alteration of genomic imprinting opens the door for an oocyte to exhibit characteristics similar to a sperm, allowing it to fertilise another egg. This can be achieved by inducing the expression of genes typically found in sperm but silenced in eggs, or conversely, by silencing genes imprinted in sperm and expressed in eggs. This groundbreaking hypothesis was initially validated by a group of scientists in 2004.[17] They switched on genes expressed in the sperm by modifying the genome of a murine egg, subsequently fertilising it with another unmodified egg (figure 1A). The

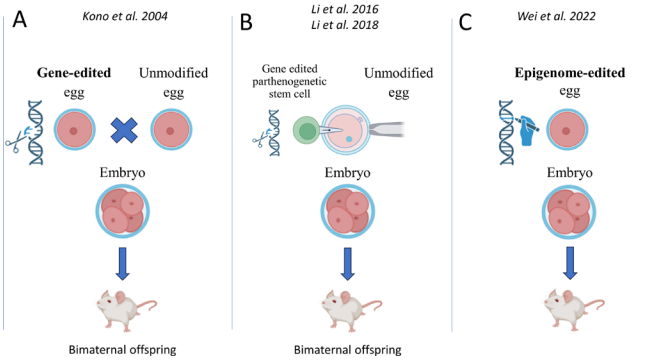

Figure 1 Schematic representation depicting the processes published in the scientific literature related to the generation of offspring solely from female mice.

ensuing embryos were successfully implanted, resulting in the birth of a healthy and fertile female offspring. This was done by deleting a specific genomic region imprinted in eggs, which in turn enabled the expression of paternal genes. Comparable breakthroughs occurred in 2016 and 2018, where specific maternal regions were deleted from the egg genome, facilitating fertilisation and the birth of bimaternal mice.[18 19] Notably, these experiments required gene editing in parthenogenetic stem cells (obtained from murine eggs) to remove maternal imprinted regions to allow the expression of paternal genes (figure 1B). However, a significant advancement emerged in 2022 with the alteration of oocyte imprinting through epigenome editing.[20] In this approach, paternal imprinting was successfully mimicked without any alteration or addition of DNA sequences (see figure 1C). By switching on and off specific imprinted genes through the addition and removal of specific methyl groups to their regions, the genetic information remained intact in the offspring's genome, as opposed to earlier experiments. In this experiment, only one egg was required to induce its activation and progress to the embryo stage, instead of the two eggs already used in the above-mentioned experiments. The results were consistent with previous studies, leading to the birth of healthy and fertile offspring in mice, devoid of apparent serious complications. Noteworthy is the discussion of the resulting offspring's sex. In humans, sex determination is contingent on the presence or absence of the Y chromosome. Given that only sperm can carry this chromosome, fusion of two oocytes in an embryo invariably yields an XX chromosomal combination, indicating the female sex.

While the mechanism of requiring opposite-sex cells for fertilisation is shared across mammals, some other species, such as bees and lizards, are capable of fertilising eggs in the absence of sperm through a process known as parthenogenesis.[21–24] In parthenogenesis, an egg is activated, developing into an embryo in the absence of sperm. Parthenogenesis can be artificially induced in mammals, including humans, although it almost always results in implantation failure.[25–28] This challenge arises from the genomic imprinting of opposite-sex genomes.[29] However, it is worth to note that parthenogenesis is not identical to the above-mentioned process. In the previous experiments (figure 1A,B), two eggs were required to fuse in order to reach the embryo stage. On the opposite, in parthenogenesis only a single egg is activated to reach this stage (figure 1C).

These advancements might prompt us, as a society, to contemplate the feasibility of a similar extrapolation in human oocytes, potentially offering lesbian couples the opportunity for biological reproduction without altering the offspring's genome. While the ethics of using gene editing for reproductive purposes[30 31] or exploring alternative cell sources like artificial gametes[32 33] have been discussed in bioethics, the use of epigenome editing for reproductive purposes remains largely uncharted.[34] It is worth to note that, while epigenome editing also allows the generation of embryos from a single edited egg, it can also be used to mimic sperm imprinting. In this context, epigenome editing could be used to obtain embryos by fusing edited and unmodified eggs, as obtained in the experiments involving gene editing.[17] In this study, I examine for the first time whether epigenome editing for enabling same-sex reproduction may potentially harm anyone and whether we should permit this technique as a means only for lesbian couples to achieve genetically related offspring. Whether it should be permissible to use epigenome editing in single eggs to allow solo or single reproduction remains to be explored.

INTERROGATING CLAIMS OF HARM IN THE INDIVIDUAL AND SOCIAL CONTEXT

In order to address the bioethical considerations arising from the utilisation of epigenome editing in same-sex reproduction, a pivotal question emerges: is anyone wronged in this process? When viewed from the perspective of the children conceived through this method, it becomes challenging to argue that they are subjected to any harm. Indeed, it seems implausible that an individual could be wronged merely by virtue of the gametes contributing to the creation of the initial embryo. If the person develops from an embryo that undergoes a pregnancy similar to a conventional embryo formed from an egg and sperm, what significant distinction can be drawn? In terms of the pregnancy process, it becomes apparent that both traditional embryos and those generated from two eggs would be virtually indistinguishable. However, more empirical data are required to asses this statement in a solid manner.[20] Furthermore, it is worth noting that an alternative technique already exists for producing human embryos without the need of either eggs or sperm: nuclear transfer (cloning).[35 36] Although cloning raises its own array of ethical concerns regarding to identity, privacy and safety, none of these revolve around the absence of traditional sex cells in the embryo's formation.[37–39] From the current study, it can be claimed that an edited egg would mimic the behaviour of sperm, and from the moment of fertilisation onward, the resulting embryo seems to function no differently from a traditional one.[20] Thus, it becomes increasingly challenging to argue that employing epigenome editing for reproductive purposes could wrong the prospective individual.

In addition, considering the non-identity problem, many authors claim that existence is generally preferable to non-existence, and actions causing existence cannot harm.[40–46] In this context, I support this assertion while assuming that epigenome editing performed on one of the eggs would not have detrimental effects on the potential offspring. In fact, there are indications to support this assumption. In the above-mentioned experiment involving offspring from eggs with altered imprinting, the resulting mice were not only healthy but also fertile and led to subsequent offspring.[20] Then, it is reasonable to expect that embryos resulting from the modification of imprinting in human eggs would not carry major health burdens. Some may argue that these experiments were conducted in mice, and thus, cannot definitively be extrapolated to humans. While this argument has merit, it is worth noting that it could have similarly precluded the development of IVF, which was initially assessed for safety in an animal model. At this juncture, there is no evidence to suggest that IVF is not associated with any age-related disorders,

simply because there are no individuals conceived through IVF who have reached old age.[47–49] Nonetheless, previous data from animal models, indicating no serious health issues, supported the application of IVF with human cells.[50–52] Therefore, further experiments in animals are essential to confirm that epigenome editing poses no harm in the context of reproductive procedures. If further empirical evidence on safety is accumulated, this would serve as compelling evidence that the resulting offspring is not subjected to harm.

Another important aspect to consider is the naturalness of the prospective offspring. They would be the result of non-natural embryos, which would never naturally come into existence through typical biological mechanisms. This aspect, often associated with the naturalistic fallacy, has been extensively explored by other authors, particularly in the context of artificial gametes.[53–57] They conclude that no moral properties should be applied to natural reproduction to be opposed to ART. Thus, the fact that epigenome editing is an artefactual reproductive method should not discourage its application. I agree with them that actions in the realm of medicine cannot be morally evaluated solely through a naturalistic lens. However, even when we set aside the naturalistic fallacy, it is worth noting that parthenogenesis, a process enabling reproduction without fertilisation, is an evolutionary mechanism that traces back to ancestors from other species.[25] This observation raises an intriguing avenue of inquiry—how the resurgence of ancient biological mechanisms (a phenomenon referred to as atavism[58 59]), which were once shared by our ancestors, might have ethical implications within the context of biological reproduction and even biological enhancement by introducing novel technologies

On the other hand, it is essential to examine the potential harm from the perspective of the prospective parents. In many countries, lesbian couples have the option to adopt children. It would seem counterintuitive to claim that these couples could be wronged by choosing to raise their genetically related children instead. In fact, this innovative technique would not even challenge conventional notions of parenthood or family structures. Many countries also permit adoption by non-traditional family units, such as single mothers or fathers, genetic relatives such as grandparents and more. Therefore, neither the prospective offspring nor the parents would be wronged by the decision to have genetically related children in the case of same-sex couples. Additionally, another dimension to be explored on the harm dimension are those commonly referred to ART, being their availability and costs.[60 61] Ultimately, epigenome editing for reproductive purposes would alter the biological connection between prospective parents and their children in the context of same-sex couples. However, it would not disrupt the social dynamics any more than in current situations where lesbian couples adopt or raise children who are genetically related to only one partner.

A notable biological consequence of same-sex reproduction, particularly in the case of lesbian couples, is that the resulting offspring would always be of the feminine sex. This raises a legitimate question regarding whether a technique with such a pronounced sex bias should be implemented in our societies. Actually, the sex predetermination of the offspring is prohibited by the Article 14 of the Oviedo Convention,[62] which might result problematic for the legal definition of this technique. It is challenging to envision a plausible scenario in which the number of lesbian couples using epigenome editing for reproduction would be substantial enough to significantly skew the gender balance at the time of birth. A similar argument has been put forth to justify the use of prenatal genetic diagnosis (PGD) for sex selection. In such cases, proponents of sex selection programmes for preimplantation embryos have suggested imposing specific conditions and restrictions.[63 64] Nevertheless, it is worth to account that in PGD there exists the possibility to select between two sexes, whereas in epigenome editing there is only one choice. Thus, it can be considered as a direct consequence (or even side effect) of same-sex biological reproduction. Perhaps, in the context of epigenome editing for same-sex reproduction, consideration could be given to limiting its use to only one child per couple. Such a restriction could help mitigate any potential bias in the sex ratio within societies if, at some point, it were to become a concern. However, this approach would also limit the autonomy of reproduction of the prospective parents and be discriminatory against men, transgender and intersex individuals.[65 66]

However, let's consider a hypothetical scenario where the use of this reproductive technique becomes so widespread that it significantly challenges or even jeopardises the male-to-female sex ratio. In such a case, should we perceive it as a problem? The primary objective of maintaining a balanced sex ratio is to ensure the continuity of our species. However, when innovative methods exist that can guarantee this continuity even in the absence of the male sex, does it still make sense to be concerned about it? This argument gains strength if we acknowledge that reproduction is not a primary right, and thus, preserving the sex ratio should not necessarily be a global societal concern.[67 68] Moreover, it is important to recognise that various queer theories emphasise the importance of gender or self-identification over biological sex.[69] From the standpoint of these philosophical theories, the balance of biological sexes may be deemed entirely irrelevant to our society.

Therefore, there are no significant concerns regarding harm that would justify the exclusion of same-sex reproduction for lesbian couples. However, as highlighted in the introduction, the attainment of genetically related offspring can be accomplished through both gene and epigenome editing methods, despite the differences in the techniques themselves. In the following section, I will delve into the ethical acceptability of same-sex reproduction using either or both of these methods.

RESPONSIBLE APPROACHES TO SAME-SEX REPRODUCTION

I previously referenced four distinct experiments where eggs were modified to enable same-sex reproduction.[17–20] However, it is important to note that these experiments employed different strategies. In the study conducted by Kono *et al*, they deleted an imprinted region within the egg—known to be silenced, not expressed—which in turn led to the overexpression of a gene known to be expressed only in sperm, thus mimicking in the egg the sperm behaviour.[17] A similar approach was used by Li *et al* in their 2016 paper, but they replaced the egg with a stem cell for the modification.[18] Subsequently, in 2018, the same research group performed gene editing using the CRISPR tool to delete additional maternal imprinted regions, resulting in bimaternal offspring once again.[19] These three strategies are summarised in figure 1A,B. Conversely, the study led by Wei *et al* in 2022 employed a different approach known as epigenome editing.[20] They used a CRISPR/CAS variant incapable of altering the DNA sequence but capable of modifying the imprinting profile (figure 1C). Through this method, they adjusted the imprinting of the egg to make it more closely resemble that of sperm.

While the biological outcomes of both processes —genetic and epigenome editing—are similar, the question of whether either or both of them are ethically acceptable for achieving genetically related offspring for same-sex couples is a subject of

inquiry. On one hand, the use of gene editing tools to manipulate the genomes of either gametes or embryos falls under germ-line editing, as the modifications would be passed on to the offspring.[70] Consequently, the edited genetic region would be present in all the cells of prospective children and would be heritable across subsequent generations. Numerous authors have deliberated on the ethical issues stemming from transmissible genetic modifications.[30 71–74]

Some authors endorse the idea of conducting germ-line editing in a therapeutic context.[75–78] Considering that the medical objective is to mitigate or eradicate the effects of a genetic disease, they claim that the best approach would be preventing at all.[79] However, it is important to note that reproduction is a biological process, and conditions that impede it, such as infertility, are typically regarded as medical conditions.[80–83] Thus, the application of germ-line editing to facilitate same-sex reproduction may not be considered ethical, as the genetic intervention—in this case, the removal of a maternally imprinted region—would persist through multiple generations.[17–19] Nevertheless, some authors argue that even though infertility is a medical condition, same-sex couples should be regarded as socially infertile.[84] This distinction is used to support certain technologies, such as the generation of artificial gametes from stem cells, for reproductive purposes.[85] However, a critical differentiation can be made in the case of artificial gamete generation: the resulting offspring would not be inherently different from those generated using traditional gametes.[86–88] Conversely, with the permanent deletion of maternally imprinted regions, offspring would have reduced chances of reproducing through natural methods, as only half of their eggs would be fertile (while the other half inherits the deleted regions, and thus would not become viable since this deletion in eggs preclude them to properly being fertilised by a sperm). Consequently, it becomes challenging to justify the consequences on the offspring derived from gene editing techniques for reproductive purposes, particularly when considering that reproduction is not universally recognised as an inherent right. On the other hand, epigenome editing would be more justified since the above-mentioned deleterious effects do not take place.

On the other hand, epigenome editing is a technique that remains relatively uncharted in the realm of bioethics.[34 89] In this approach, DNA sequences themselves are not altered; instead, the focus is on how these sequences are interpreted and regulated by the cellular machinery. Epigenetic changes are notably malleable, and various mechanisms exist for epigenome remodelling.[90] This flexibility implies that these alterations are not permanent across generations, as opposed to the modifications induced by gene editing. Epigenome editing can be seen as a transient modification in contrast to the permanent ones induced by genetic editing, addressing some of its ethical concerns, as the offspring resulting from epigenome editing would not be genetically affected. In fact, some authors advocate for the use of epigenome editing precisely because it can lead to similar effects than gene editing without genetically affecting the resulting individual,[89 91] presenting a promising avenue for genetic intervention with fewer ethical dilemmas. Even if this makes epigenome editing far more acceptable than human germ-line editing, similar ethical concerns might arise, like the persistency of off-target effects.[34 89 92] More research is needed in the safety and clinical aspect of this technique, to the moment only performed in rodents, to determine the likelihood of these effects. Whenever the risks outweigh the benefits, then safer alternatives like adoption or gamete donation should be considered.

In this section, I have argued that some methods aimed at enabling same-sex reproduction, like gene editing, are not ethically acceptable. While this technique applied to the germline cannot be ethically justified for reproductive purposes, a novel approach involving epigenome editing holds promise. This method could potentially achieve bimaternal genetically related offspring while addressing most of the ethical concerns associated with traditional gene editing techniques, like the persistency of the modification across generations. Importantly, epigenome editing would not alter the genome of the offspring.[90 93] Consequently, epigenome editing for reproductive purposes emerges as an ethically acceptable means to facilitate same-sex reproduction among lesbian couples.

REPRODUCTIVE EPIGENOME EDITING THROUGH A FEMINIST LENS

One of the groundbreaking aspects of same-sex reproduction among lesbian couples is its challenge to our traditional concept of reproduction. It is imperative to explore this concept through the lens of contemporary feminist theories, especially in light of the potential for epigenome editing to make same-sex reproduction a reality in humans.

A recurring ethical issue that arises in discussions involving gay same-sex or even opposite-sex couples, when one partner cannot gestate, is the consideration of surrogacy.[94 95] Many feminist authors view surrogacy as the commodification of women's bodies, reducing them to fetal containers, and thus, they question its ethical acceptability for facilitating reproduction within these couples.[96–98] However, this ethical concern may not necessarily apply to lesbian couples, as either partner would have the capability to gestate prospective children. Nevertheless, epigenome editing of eggs also opens the door to further ethical exploration on questions that could arise if a third-party woman serves as a surrogate. It could be the case that both of the partners cannot gestate due to lack of uterus or implantation issues.[99] Depending on the legislation of certain countries, the surrogate may be recognised as the legal mother, potentially leading to unconventional family structures that involve three women.

Another intriguing connection can be established between same-sex reproduction and the theories surrounding self-identification of gender. The epigenome editing technique fundamentally challenges the conventional concept of reproduction on the sex cell identity. In this novel approach, an egg obtained from a woman can be epigenetically edited to behave like a sperm from a genetic perspective. This introduces an additional layer of disruption to the traditional correlation between biological sex and gender identity.[100 101] However, some authors, such as Pruski,[102] argue against the use of artificial gametes derived from opposite-sex individuals. This intriguing junction between reproductive technology and the fluidity of gender identity calls for further philosophical research that extends beyond the scope of bioethics, delving into the complex and evolving understanding of the relationship between sex and gender in contemporary society.

Another aspect worth analysing from this perspective is whether it is ethically acceptable to allow lesbian couples to pursue biological reproduction when it is not possible with male gametes. It is worth noting that the research conducted by Li *et al* also involved modifying the imprinting of sperm to enable same-sex reproduction when crossed with male germ cells.[19] However, the offspring resulting from bipaternal males dies shortly after birth, indicating that this process is not compatible with sustaining life. Nevertheless, the fact that same-sex reproduction might not be feasible for

gay couples does not delegitimise the pursuit of lesbian reproduction.[103] There is no inherent requirement for both sexes to possess the same biological properties, as exemplified by the process of pregnancy. In a recent publication, Smajdor proposed two alternative approaches for surrogacy in pregnancy, involving the bodies of either women or men as potential surrogates.[104] Interestingly, the critique surrounding these proposals rarely centred on the idea that men could potentially carry pregnancies. Instead, no attention was paid to the rights or responsibilities associated with the possibility that men could equally carry pregnancies. Then, it seems clear that precluding the use of a technique suited only for a specific sex but not the opposite, would not only halt scientific advances but also lead to harm, as previous authors denoted.[103] Thus, this argument should not serve as a critique against same-sex reproduction but rather as a rationale for continuing research into the possibility of same-sex reproduction involving men.

In light of certain feminist viewpoints, it can be argued that epigenome editing offers an ethically sound venue for enabling same-sex reproduction among lesbian couples. Moreover, this innovative technique challenges our traditional understanding of concepts such as gender self-identification and the interplay between biological sex and gender, particularly in terms of gamete production.[105 106] To date, therefore, there is a pressing need for further philosophical exploration in this intersection between epigenome editing and feminist views, since eggs (female germ cells) can be epigenetically edited to behave like sperm (male germ cells).

Finally, epigenome editing leading to bimaternal offspring not only challenged several traditional notions concerning our understanding of reproduction but also biological definitions. Indeed, the generation of embryos from two eggs prompts a call for further research into a revised definition of the human embryo, one that encompasses a broader range of biological entities with the potential to develop into a newborn.[107] This is a point that has been advanced by numerous researchers. Since the biological definition of an embryo seems to be constrained to the product of an egg activated by a sperm, it seems that embryonic structures and fetal entities can be achieved in the absence of sperm, as noted through this article, and even in absence of both gametes.[108–111]

CONCLUSIONS

In conclusion, the ethical landscape surrounding same-sex reproduction through epigenome editing is discussed here for the first time. From a global ethical standpoint, it becomes evident that this innovative technique offers an ethically acceptable means for lesbian couples to achieve genetically related offspring. The absence of significant harm to the prospective children, the potential to overcome ethical concerns associated with traditional gene editing, and the alignment with certain feminist perspectives contribute to the overall normativity of this approach.

Moreover, the advent of same-sex reproduction challenges conventional concepts of reproduction itself, prompting a need for redefining our understanding of the human embryo to encompass a wider range of biological entities capable of developing into newborns. The discussion on epigenome editing for same-sex reproduction transcends bioethics and delves into the realms of gender self-identification, the fluidity of reproductive roles, and the very essence of what it means to create a family. To sum up, the ethical and philosophical deliberations on same-sex reproduction through epigenome editing emphasise the horizons of the bioethical research in reproduction.

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REFERENCES

1 Siu KK, Serrão VHB, Ziyyat A, *et al*. The cell biology of fertilization: gamete attachment and fusion. *J Cell Biol* 2021;220:e202102146.
2 Bianchi E, Wright GJ. Sperm meets egg: the genetics of mammalian fertilization. *Annu Rev Genet* 2016;50:93–111.
3 Ethics Committee of the American Society for Reproductive Medicine. Access to fertility treatment by gays, lesbians, and unmarried persons. *Fertil Steril* 2009;92:1190–3.
4 Cavaliere G. Involuntary childlessness, suffering, and equality of resources: an argument for expanding state-funded fertility treatment provision. *J Med Philos* 2023;48:335–47.
5 Núñez A, García D, Giménez-Bonafé P, *et al*. Reproductive outcomes in Lesbian couples undergoing reception of oocytes from partner versus autologous in vitro fertilization/intracytoplasmic Sperm injection . *LGBT Health* 2021;8:367–71.
6 Brandão P, de Pinho A, Ceschin N, *et al*. ROPA – lesbian shared in vitro fertilization – ethical aspects. *Eur J Obstet Gynecol Reprod Biol* 2022;272:230–3.
7 Cavaliere G, Palacios-González C. Lesbian motherhood and mitochondrial replacement techniques: reproductive freedom and genetic kinship. *J Med Ethics* 2018;44:835–42.
8 Palacios-González C, Cavaliere G. Yes' to mitochondrial replacement techniques and lesbian motherhood: a reply to Françoise Baylis. *J Med Ethics* 2019;45:280–1.
9 Noohi F, Ravitsky V, Knoppers BM, *et al*. Mitochondrial replacement therapy: in whose interests *J Law Med Ethics* 2022;50:597–602.
10 Jellerette-Nolan T, Cooper AR, Doody KJ, *et al*. Real-world experience with Intravaginal culture using INVOCELL: an alternative model for infertility treatment. *F S Rep* 2021;2:9–15.
11 Manoj G, Anjali K, Presannan A, *et al*. Epigenetics, Genomics imprinting and non-coding Rnas. *Prog Mol Biol Transl Sci* 2023;197:93–104.
12 Zeng Y, Chen T. DNA methylation reprogramming during mammalian development. *Genes (Basel)* 2019;10:257.
13 Tucci V, Isles AR, Kelsey G, *et al*. Genomic imprinting and physiological processes in mammals. *Cell* 2019;176:952–65.
14 Barlow DP, Bartolomei MS. Genomic imprinting in mammals. *Cold Spring Harb Perspect Biol* 2014;6:a018382.
15 Wilkins-Haug L. Epigenetics and assisted reproduction. *Curr Opin Obstet Gynecol* 2009;21:201–6.
16 Gayon J. From Mendel to epigenetics: history of genetics. *C R Biol* 2016;339:225–30.
17 Kono T, Obata Y, Wu Q, *et al*. Birth of parthenogenetic mice that can develop to adulthood. *Nature* 2004;428:860–4.
18 Li Z, Wan H, Feng G, *et al*. Birth of fertile bimaternal offspring following intracytoplasmic injection of parthenogenetic Haploid embryonic stem cells. *Cell Res* 2016;26:135–8.
19 Li Z-K, Wang L-Y, Wang L-B, *et al*. Generation of bimaternal and bipaternal mice from hypomethylated haploid ESCs with imprinting region deletions. *Cell Stem Cell* 2018;23:665–76.
20 Wei Y, Yang CR, Zhao ZA. Viable offspring derived from single unfertilized mammalian Oocytes. *Proc Natl Acad Sci U S A* 2022;119:e2115248119.
21 Sperling AL, Glover DM. Parthenogenesis in dipterans: a genetic perspective. *Proc R Soc B* 2023;290.
22 Thomalla JM, Wolfner MF. Reproductive biology: a genetic recipe for parthenogenesis. *Curr Biol* 2023;33:R904–6.
23 Kratochvíl L, Vukić J, Červenka J, *et al*. Mixed-sex offspring produced via cryptic parthenogenesis in a lizard. *Mol Ecol* 2020;29:4118–27.
24 Barley AJ, Cordes JE, Walker JM, *et al*. Genetic diversity and the origins of parthenogenesis in the teiid lizard Aspidoscelis Laredoensis. *Mol Ecol* 2022;31:266–78.
25 Lampert KP. Facultative parthenogenesis in vertebrates: reproductive error or chance *Sex Dev* 2008;2:290–301.
26 Rougier N, Werb Z. Parthenogenesis in mammals. *Mol Reprod Dev* 2001;59:468–74.
27 Liang R, Wang Z, Kong X, *et al*. Differentiation of human parthenogenetic embryonic stem cells into functional hepatocyte-like cells. *Organogenesis* 2020;16:137–48.
28 Sidhu GS, Conner JA, Ozias-Akins P. Controlled induction of parthenogenesis in transgenic rice via post-translational activation of Psasgr-BBML *Front Plant Sci* 2022;13:925467.
29 Kono T. Genomic imprinting is a barrier to parthenogenesis in mammals. *Cytogenet Genome Res* 2006;113:31–5.
30 Schleidgen S, Dederer H-G, Sgodda S, *et al*. Human germline editing in the era of CRISPR-CAS: risk and uncertainty, inter-generational responsibility, therapeutic legitimacy. *BMC Med Ethics* 2020;21:87.
31 Morange M. Human Germline editing: a historical perspective. *Hist Philos Life Sci* 2017;39:34.

32 Newson AJ, Smajdor AC. Artificial gametes: new paths to parenthood *J Med Ethics* 2005;31:184–6.
33 Testa G, Harris J. Ethics and synthetic gametes. *Bioethics* 2005;19:146–66.
34 Alex K, Winkler EC. Comparative ethical evaluation of epigenome editing and genome editing in medicine: first steps and future directions. *J Med Ethics* 2023. 10.1136/jme-2022-108888 [Epub ahead of print 1 Aug 2023].
35 Matoba S, Zhang Y. Somatic cell nuclear transfer reprogramming: mechanisms and applications. *Cell Stem Cell* 2018;23:471–85.
36 Gouveia C, Huyser C, Egli D, *et al*. Lessons learned from somatic cell nuclear transfer. *Int J Mol Sci* 2020;21:2314.
37 Sparrow R. Cloning, Parenthood, and genetic relatedness. *Bioethics* 2006;20:308–18.
38 Harris J. On cloning / John Harris. 2004. Available: https://books.google.com/books/about/On_Cloning.html?hl=fr&id=E2cEHdR51H4C [Accessed 22 Sep 2023].
39 Kass L. *The wisdom of repugnance: why we should ban the cloning of humans*. Valparaiso Univ Law Rev, 2011: 32. Available: https://scholar.valpo.edu/vulr/vol32/iss2/12
40 Margolis J, Parfit D. Reasons and persons. *Philosophy and Phenomenological Research* 1986;47:311.
41 Brock DW. The non-Identity problem and genetic harms – the case of wrongful handicaps. *Bioethics* 1995;9:269–75.
42 Woollard F. Have we solved the non-identity problem *Ethic Theory Moral Prac* 2012;15:677–90.
43 Parfit D. Future people, the non-identity problem, and person-affecting principles. *Philosophy & Public Affairs* 2017;45:118–57.
44 Bennett R. Why the principle of procreative beneficence must work much harder to justify its eugenic vision. *Bioethics* 2014;28:447–55.
45 Savulescu J. Is there a 'right not to be born'? Reproductive decision making, options and the right to information. *Arch Dis Child Fetal Neonatal Ed* 2002;87:F72–4.
46 Steinbock B, McClamrock R. When is birth unfair to the child *Hastings Cent Rep* 1994;24:15–21.
47 Hyman DA, Silver C. IVF shared-risk programs. *J Law Med Ethics* 1998;26:79–80.
48 Deech R, Smajdor A. *From IVF to immortality: controversy in the era of reproductive technology*. 2007.
49 Smajdor A, Villalba A. The ethics of cellular reprogramming. *Cellular Reprogramming* 2023;25:190–4.
50 Seidel GE, Bowen RA, Kane MT. In vitro fertilization, culture, and transfer of Rabbit ova. *Fertil Steril* 1976;27:861–70.
51 Lambert RD, Hamner CE. In vitro fertilization of Rabbit eggs in oviduct secretions from different days before and after ovulation. *Fertil Steril* 1975;26:660–4.
52 Miyamoto H, Chang MC. In vitro fertilization of rat eggs. *Nature* 1973;241:50–2.
53 Smajdor A, Cutas D, Takala T. Artificial gametes, the unnatural and the artefactual. *J Med Ethics* 2018;44:404–8.
54 Cutas D, Smajdor A. Postmenopausal motherhood reloaded: advanced age and in vitro derived Gametes. *Hypatia* 2015;30:386–402.
55 Soper K. Thinking the unnatural. *Capitalism Nature Socialism* 2005;16:129–34.
56 Zwart HAE. The moral significance of our biological nature. *Ethical Perspectives* 1994;1:71–8.
57 Testa G, Harris J. Ethical aspects of ES cell-derived gametes. *Science* 2004;305:1719.
58 Hall BK. Atavisms. *Curr Biol* 2010;20:R871.
59 Lange A, Müller GB. Polydactyly in development, inheritance, and evolution. *Q Rev Biol* 2017;92:1–38.
60 Carter D, Watt AM, Braunack-Mayer A, *et al*. Should there be a female age limit on public funding for assisted reproductive technology?: differing conceptions of justice in resource allocation. *J Bioeth Inq* 2013;10:79–91.
61 Peterson MM. Assisted reproductive technologies and equity of access issues. *J Med Ethics* 2005;31:280–5.
62 Oviedo convention and its protocols - human rights and biomedicine. Available: https://www.coe.int/en/web/bioethics/oviedo-convention [Accessed 21 Nov 2023].
63 Savulescu J, Dahl E. Sex selection and preimplantation diagnosis: a response to the ethics committee of the American Society of Reproductive Medicine. *Hum Reprod* 2000;15:1879–80.
64 Dahl E. Sex selection: Laissez faire or family balancing? *Health Care Anal* 2005;13:87–90.
65 Robertson JA, John A. *Children of choice: freedom and the new reproductive technologies*. 1994: 281.
66 Robertson JA. Procreative liberty in the era of Genomics. *Am J Law Med* 2003;29:439–87.
67 Hall GA. Reproduction misconceived: why there is no right to reproduce and the implications for ART access. *J Med Ethics* 2022:jme–2022
68 Hall GA. A little bit pregnant: towards a pluralist account of non-sexual reproduction. *J Med Ethics* 2023. 10.1136/jme-2022-108858 [Epub ahead of print 13 Apr 2023].
69 Ásta Á. Categories we live by: the construction of sex, gender, race, and other social categories. *Categ We Live By* 2018.
70 Bekaert B, Boel A, Cosemans G, *et al*. CRISPR/CAS gene editing in the human Germline. *Semin Cell Dev Biol* 2022;131:93–107.
71 Coller BS. Ethics of human genome editing. *Annu Rev Med* 2019;70:289–305.
72 Gyngell C, Douglas T, Savulescu J. The ethics of Germline gene editing. *J Appl Philos* 2017;34:498–513.
73 Guttinger S. Editing the reactive genome: towards a postgenomic ethics of Germline editing. *J Applied Philosophy* 2020;37:58–72.
74 Gumer JM. The wisdom of Germline editing: an ethical analysis of the use of CRISPR-Cas9 to edit human embryos. *New Bioeth* 2019;25:137–52.
75 de Miguel Beriain I. Should human germ line editing be allowed? Some suggestions on the basis of the existing regulatory framework. *Bioethics* 2019;33:105–11.
76 Ranisch R. Germline genome editing versus preimplantation genetic diagnosis: is there a case in favour of Germline interventions *Bioethics* 2020;34:60–9.
77 Savulescu J, Gyngell C, Douglas T. Germline Edits: trust ethics review process. *Nature* 2015;520:623.
78 Cavaliere G. Genome editing and assisted reproduction: curing embryos, society or prospective parents *Med Health Care and Philos* 2018;21:215–25.
79 Lundberg AS, Novak R. CRISPR-CAS gene editing to cure serious diseases: treat the patient, not the germ line. *Am J Bioeth* 2015;15:38–40.
80 Kukla R. Infertility, epistemic risk, and disease definitions. *Synthese* 2019;196:4409–28.
81 Pittman SP, Alam SM, Rosell T, *et al*. Infertility counseling and misattributed paternity: when should physicians become involved in family affairs. *J Clin Ethics* 2022;33:151–6.
82 Gunes S, Esteves SC. Role of Genetics and Epigenetics in male infertility. *Andrologia* 2021;53.
83 Bulletti C, Coccia ME, Battistoni S, *et al*. Endometriosis and infertility. *J Assist Reprod Genet* 2010;27:441–7.
84 Lo W, Campo-Engelstein L. Expanding the clinical definition of infertility to include socially infertile individuals and couples. *Reprod Ethics II* 2018:71–83.
85 Notini L, Gyngell C, Savulescu J. Drawing the line on in vitro gametogenesis. *Bioethics* 2020;34:123–34.
86 Cutas D, Dondorp W, Swierstra T, *et al*. Artificial Gametes: perspectives of geneticists, ethicists and representatives of potential users. *Med Heal Care Philos* 2014;17:339–45.
87 Moreno I, Míguez-Forjan JM, Simón C. Artificial gametes from stem cells. *Clin Exp Reprod Med* 2015;42:33–44.
88 Zhang P-Y, Fan Y, Tan T, *et al*. Generation of artificial Gamete and embryo from stem cells in reproductive medicine. *Front Bioeng Biotechnol* 2020;8:781.
89 Akatsuka K, Sasaki-Honda M, Sawai T. Ethical framework for next-generation genome and epigenome editing. *Am J Bioeth* 2020;20:32–6.
90 Eckersley-Maslin MA, Alda-Catalinas C, Reik W. Dynamics of the epigenetic landscape during the maternal-to-Zygotic transition. *Nat Rev Mol Cell Biol* 2018;19:436–50.
91 Lewens T. Blurring the germline: genome editing and transgenerational epigenetic inheritance. *Bioethics* 2020;34:7–15.
92 Huerne K, Palmour N, Wu AR, *et al*. Auditing the editor: A review of key translational issues in epigenetic editing. *The CRISPR Journal* 2022;5:203–12.
93 Holtzman L, Gersbach CA. Editing the epigenome: reshaping the genomic landscape. *Annu Rev Genomics Hum Genet* 2018;19:43–71.
94 Beier K. Surrogate motherhood: a trust-based approach. *J Med Philos* 2015;40:633–52.
95 Teman E. Embodying surrogate motherhood: pregnancy as a Dyadic body-project. *Body & Society* 2009;15:47–69.
96 Munro VE. Surrogacy and the construction of the maternal-foetal relationship: the feminist dilemma examined. *Res Publica* 2001;7:13–37.
97 Robinson S. Full Surrogacy now: feminism against the family by Sophie Lewis. *IJFAB* 2020;13:199–203.
98 Yanagihara Y. Reconstructing feminist perspectives of women's bodies using a globalized view: the changing Surrogacy market in Japan. *Bioethics* 2020;34:570–7.
99 Guntram L, Williams NJ. Positioning uterus transplantation as a 'more ethical' alternative to Surrogacy: exploring Symmetries between uterus transplantation and Surrogacy through analysis of a Swedish government white paper. *Bioethics* 2018;32:509–18.
100 Bex-Priestley G. Gender as name. *JESP* 2022;23.
101 Jenkins K. Toward an account of gender identity. *Ergo, an Open Access Journal of Philosophy* 2018;5.
102 Pruski M. The relationship of Gametes to those who Procreate and its impact on artificially generated Gamete Technologies. *Ethics Med* 2017;33:27–41.
103 Harris J. *Enhancing evolution*. 2010.
104 Smajdor A. Whole body gestational donation. *Theor Med Bioeth* 2023;44:113–24.
105 Räsänen J, Smajdor A. The complex case of Ellie Anderson. *J Med Ethics* 2022;48:217–21.
106 Kirejczyk M. On women, egg cells and embryos. *European Journal of Women's Studies* 2008;15:377–91.
107 De Miguel Beriain I, Rueda J, Villalba A. Re-defining the human embryo. *EMBO Rep* 2024;25:467–70.
108 Ball P. What is an embryo? Scientists say definition needs to change. *Nature* 2023;620:928–9.
109 Rivron NC, Martinez Arias A, Pera MF, *et al*. An ethical framework for human embryology with embryo models. *Cell* 2023;186:3548–57.
110 Blasimme A, Sugarman J. Human stem cell-derived embryo models: toward ethically appropriate regulations and policies. *Cell Stem Cell* 2023;30:1008–12.
111 Villalba A, Rueda J, de Miguel Beriain Í. Synthetic embryos: a new Venue in ethical research. *Reproduction* 2023;165:V1–3.