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GENOME EDITING, HUMAN CLONING, IN VITRO GAMETES AND ARTIFICIAL WOMB: TOWARDS FUTURE SCENARIOS, NEW DILEMMAS AND RESPONSIBILITIES.
GUEST EDITOR'S INTRODUCTION

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ABSTRACT
In the future human reproduction could radically change. Today the birth occurs always through the fertilisation of an egg cell by the spermatozoon: tomorrow people could be born by cloning from a somatic cell or by parthenogenesis, without the need for a spermatozoon. Moreover, for the moment pregnancy may only occur in the woman's body: yet in the future, we could also have artificial wombs able to grow an embryo up to the birth. Finally, today our genetic heritage is determined by chance, while in the future we could choose our children's DNA: at that point, we could not only correct important anomalies, but even enhance the future generations' dispositions and capacities. New reproductive technologies like cloning, parthenogenesis, artificial gametes and genome editing may contribute to correcting some important natural injustices. At the same time, we must also be aware that introducing new reproductive technologies may increase social injustice and negatively affect our 'reproductive freedom'.

KEYWORDS
Bioethics, reproduction, cloning, genome editing, freedom

In the future human reproduction could radically change. Until about forty years ago, birth was only possible via a sexual relationship: then in 1978 children started to be born not only sexually, but also with assisted reproduction. Now, it does not matter which technique is used: the birth of a new person occurs always

through the fertilisation of an egg cell by the spermatozoon. However, tomorrow people could be born by cloning from a somatic cell or by parthenogenesis, only from an egg cell and without the need for a spermatozoon: it could suffice to stimulate an oocyte electrically or chemically, and there you are: the cell would start to split like an embryo. Indeed, "parthenogenetic activation of human oocytes rescued from infertility treatments results in embryos which are comparable to their biparental counterparts.[1]" Further, we could obtain several embryos from one through embryo splitting, while, mainly for the benefit of one who cannot produce or has no gametes left, we could get both oocytes and sperm from body cells. Moreover, for the moment pregnancy may only occur in the woman's body: we are able to conceive a human embryo in a laboratory and can also continue its development for a limited number of days[2], but if we then want the embryo to complete its development, we must transfer it into a woman. Yet in the future, we could also have machines (that is, artificial wombs) able to continue the birth of a human embryo up to the birth[3]: the parents could observe its development from home and maybe also interact with it through technology allowing signals to be broadcast from afar. Finally, today our genetic heritage is determined by chance, while in the future we could choose our children's DNA: at that point, we could not only correct important anomalies, but even enhance the future generations' dispositions. For example, we could supply them with greater resistance to diseases, but maybe we could also enhance their cognitive and moral attitudes. We already have genome editing, which we use to modify animals and plants: using them to modify humans does not appear to be a mirage. First we must continue research on genome editing in human embryos: but once these interventions are safe, we could use them clinically, with important advantages for both those who will be born and society as a whole.[4]

[1] A. Bos-Milkich et al., *Parthenogenesis and Human Assisted Reproduction*, "Stem Cells International", 2016, 2, pp. 1-8, p. 6.

[2] A. Deglincerti et al., *Self-Organization of the In Vitro Attached Human Embryo*, "Nature", DXXXIII, 7602, 2016, pp. 251-263; M. Nasila Shahbazi et al., *Self-Organization of the Human Embryo in the Absence of Maternal Tissues*, "Nature Cell Biology", XVIII, 6, 2016, pp. 700-710.

[3] E. C. Romanis, *Artificial Womb Technology and the Frontiers of Human Reproduction: Conceptual Differences and Potential Implications*, "Journal of Medical Ethics", 2018, 44, pp. 751-755.

[4] H. T. Greely, *The End of Sex and the Future of Human Reproduction*, Harvard University Press 2016.

The articles gathered in this special issue face these new reproductive scenarios. The themes considered concern the use of genome editing techniques to care for or prevent important diseases, the moral acceptability of genetics interventions aimed to improve the abilities of future generations, the limits of state intervention in matters of reproductive autonomy (for example, is state eugenics compatible with a 'liberal society'?), the moral responsibilities of prospective parents towards their children (do prospective parents have a duty to select the healthiest and luckiest possible children?) and the effects of the biomedical revolution on society and non-human animals. These are very complex issues on which there is a great deal of disagreement. Religions could once offer a precise answer to each of these questions: in secularised societies, religion is no longer a moral reference point and even the faithful no longer seem to trust it to solve the new moral dilemmas. Moreover, religions do not always converge on the main questions at the heart of the current bio-technological revolution. For example, regarding the possibility of performing interventions on the genome of the embryo, not only does each religion have a different position from other religions, but each individual religion produces discordant opinions.

Let us start from the hypothesis that cloning, parthenogenesis, gametes in vitro, the artificial uterus and genome editing interventions are safe. Any person may have the chance to enjoy access to these technologies, and the person born does not run any risk of suffering serious genetic anomalies or having an existence worse than other children have. We shall, then, leave aside some moral objections which were in the past made against assisted reproduction techniques: for example, that they are immoral because conceiving a human embryo in a test tube would not be natural or because, as Catholic Church says, humans should only be conceived through a sexual intercourse. In fact, establishing what is natural is a highly complex philosophical question: further, not only is that which is natural not necessarily good (consider earthquakes, but also disease: they are natural phenomena, but there is nothing good in the fact that an earthquake occurs or that a person gets ill and is condemned to suffering for the rest of his days), but there are things which are not natural but are, at the same time, good (there is nothing natural in removing an organ from a body and transferring it into another human being; in fact, the intervention may save someone's life). Further, there seems to be nothing intrinsically immoral in *in-vitro* reproduction: maintaining that human reproduction should not be separated from sexuality is like stating that using means of transport is immoral. Once, we could move from

one place to another only by walking, but this does not make cycling, riding a horse or driving a car intrinsically immoral. In the same way, until a few years ago we only had children sexually, but that does not prove that assisted reproduction is morally unacceptable. Then, it is not true that behind the choice of assisted reproduction, there can only be immoral reasons or motivations, such as, for example, a tendency to consider a child as a mere means for one's own happiness. We do not fall into any contradiction in imagining a virtuous person (for example, loving and generous) who turns to assisted reproduction.

New reproductive technologies like cloning, parthenogenesis, artificial gametes and genome editing[5] may contribute to correcting some natural injustices. For example, they may help people who cannot reproduce sexually (they have no gametes) or lack 'viable' spermatozoa or egg cells. We can, for example, think of a lesbian couple: the nuclear DNA of a woman's somatic cell could be transferred by cloning into the other's egg cell. The girl born would receive her genetic material from both women: nuclear DNA from the first and mitochondrial DNA from the second. Moreover, two men could have a child by turning to artificial or *in vitro* oocytes: from a man's somatic cells they could obtain first pluripotent stem cells and then 'viable' oocytes to be fertilised with the other man's sperm. The child born would have as parents not one man and one woman, but two men, because – yes – both would contribute to his genetic code in the same way. Further, singles could have the chance to have a biological child with no longer the need to turn to a spermatozoon or egg cell donor. At the moment one can only have a child with the contribution from another person: tomorrow, any person could have a biological child on his or her own. A man could fertilise the egg cells produced by his own somatic cells with his own sperm, while a woman could turn to reproductive cloning: transferring the DNA of one of her cells into her oocyte would suffice. In both cases, the one coming into the world would only have one biological parent. And with in-vitro gametes, another unfair condition could be removed: now, old men can have a biological child, while after the menopause, women can no longer have a biological child: they can adopt one or reproduce with a donor's egg cells, but if they do not have frozen oocytes, they can no longer have a child with their genome. The development of in-vitro or artificial gametes from somatic cells would give a woman a chance to have a child with her DNA even after the menopause. In addition, as Anna Smajdor explains,

[5] J. Kozubek, *Modern Prometheus: Editing the Human Genome with Crispr-Cas9*, Cambridge University Press 2018.

the production of gametes from skin cells would allow one to have gametes from people who died, without performing interventions that could violate their bodily integrity or dignity. The reason is simple: today, gathering the spermatozoa from someone deceased, at the partner's request, requires the insertion of a probe into the anus, and then proceeding with electric discharges of ever higher voltage, until ejaculation is obtained (in the corpse), or part of the testicles must be cut, or castration practised, while tomorrow, to obtain a sample of sperm to use for reproduction, it may suffice to transform skill into sperm cells. Finally, the artificial uterus would be advantageous for both women and men. Indeed, with an artificial uterus, women – who wish to have a son (but not a birth) – would no longer be forced to have a pregnancy for nine months. But an artificial uterus would also be in men's interests, as it would allow them to enjoy the same reproductive freedom as only women have today. That is, in order to have a child, they would no longer depend on the women, but could, like women, have a child how and when they would most like to, because they could have their embryo grow in an artificial uterus.

Moreover, with genetic editing interventions, one could also correct possible genetic anomalies and in this way prevent the birth of children with serious disabilities. It is unreasonable to attribute value to any genetic condition: biodiversity could be enrichment, but other times it is also a problem. Further, if it were wrong to remove or prevent a natural condition of disability, then we should abstain from not only genetic correction interventions, but also any treatment able to cure or prevent disease. For example, let us imagine that a pill is produced that can immediately correct any disability, with no risk or side effect. Would we say that it would be wrong to produce it, put it onto the market and then let our children take it? So why should it be wrong to turn to genome editing interventions to correct genetic anomalies and thus prevent the birth of disabled people? Furthermore, we already choose the genetic code of people to be born: indeed, via assisted reproduction, we can select the embryo with the better genome. Consider, for example, the case of people carrying recessive genetic anomalies: there is one probability in four that they transmit the disease to the embryo, and one probability in two that the embryo inherits a copy of the anomaly (cystic fibrosis and sickle cell anaemia are recessive generic diseases), but if a parent carries a dominant genetic anomaly (but carries another version of the gene which does not, in contrast, cause the disease), the embryo has one probability in two of inheriting the anomaly. Then, both parents may be carriers:

in this case the probability of transmitting the anomaly rises to 75% (an example of a dominant autosomal disease is Huntington's). However, pre-implantation genetic diagnosis may serve to avoid the transmission of disease linked to mutations or anomalies of individual genes to future generations, but cannot be useful in avoiding the transmission of the disease when one of the parents carries both dominant mutations or when both parents carry the copy of the recessive mutations: in this case, we are 100% sure that the embryo will inherit the disease. Finally, when a disease depends on anomalies spread over numerous genes, it is much more difficult to 'eliminate' it through pre-implantation diagnosis: indeed, to have an embryo that does not display any of the genes responsible for the disease, we should create a huge number of embryos. Also in this particular case, the advantages of genome editing are more than evident: with genome editing it is possible to correct various genes "at once".

I am not saying that the distinction between disease and health is always clear and I recognise that sometimes the parent may have legitimate doubts about what to do in the presence of an embryo with a particular genome. Why, for example, a parent should discard an embryo with a moderate form of autism? As Elvio Baccarini and Kristina Lekić Barunčić write, a child with this form of autism will lack a sense of humour and empathy, not to mention the ability to enjoy a social life: however, it will have other abilities and dispositions, which may make his life particularly valuable. For this reason, enhancing this embryo may be morally justified, but only as long it does not, with the tendency to autism, remove that very ability. At the time of genome editing, prospective parents will have greater responsibility and find themselves before these dilemmas more and more: sometimes, the choices will be very difficult, but at other times, they will be easier, because genome interventions could prevent conditions of extreme suffering.

However, genome editing can be practised not only to prevent and cure disabilities, but also to modify plants' and animals' genetic codes. The market already presents several varieties of genetically modified plants with, for example, resistance to pests, insects, diseases, environmental conditions and chemical treatment, which increase the quality and quantity of the harvest. With the use of genome editing techniques, which allow far more precise and efficient interventions, even much better results may be reached. And the animals may be genetically modified so as to obtain more commercially interesting breeds, to produce therapeutic substances and tissue for implantation or obtain *in vivo* models for studying human diseases. But in the future, as Silvia Camporesi

reminds us, we could be able to produce animals whose organs may be transplanted without any rejection risk. About 20 people awaiting an organ transplant die every day in the USA alone: and statistics confirm that the shortage of organs is a humanitarian emergency. The use of animals in bio-farms could radically change this situation, because we may finally be able to count on 'human' organs from animals. But, as Silvia Camporesi wonders, is this the future we want: can we not perhaps imagine different solutions which do not assume the exploitation of animals or accept a market logic reducing the other to a mere 'means'?

The fear that the other be treated as just a means reappears in Smajdor's article: the possibility of transforming skin cells into gametes raises people's reproductive freedom. But it becomes something morally unacceptable if this occurs after death, at the request of a third party (for example, the partner) and without the person's consent. Firstly, the procedure would not be invasive; secondly, it would be not comparable to sexual violence or incompatible with respect for reproductive freedom. However, it would mark an evident tendency to reduce the person to an object. In the face of technological development, it may be easy to give in to optimism: this is why it is very important not to stop cultivating our critical thinking. This is a clear invitation we find expressed in every article of this issue. So far we have mainly considered the advantages of possible future scenarios, but the introduction of new reproductive technologies could not only correct certain unfair conditions, but may also reinforce old unfair conditions. For example, are we sure that every person will have the chance to turn to cloning, parthenogenesis, artificial gametes and genome editing interventions? As occurred with other technologies in the past, in an initial phase the costs could be high, but they may then go down and become easier to access. Further, the more the costs for these technologies go down, the more the national health service may be able to guarantee access to all citizens. But if the costs remain significant only richer people could turn to these technologies. This means that while some people may have a biological child, others will have to turn to a donor or give up having a child. The problem already presents itself in somatic genome editing, which are even now beginning to be authorised for the caring of significant diseases. Today the cost of somatic genetic editing for a rare

form of blindness is 850,000 dollars[6]: how many people can afford to pay such a high sum of money?

Also, with genome editing, there may be even more serious social injustice, because a number of people may be born with an improved genome, while others, maybe the outstanding majority of the population, would not be enhanced. The enhanced people could have a longer life, be more resistant to diseases and also have greater physical and intellectual performance, whereas people with a normal genetic code could be discriminated against as inferior or because they may seem to belong to another species. It could lead to the 'new world' described by Huxley in his novel: that is, a society rigidly divided into in castes, where people's worth and dignity are measured on the basis of the genetic inheritance they have received. There has always been social injustice, but with the development of genome editing and the possibility of correcting and/or enhancing the genome, maybe no one would still have the chance to be freed from his 'destiny'. Moreover, we could even imagine 'universal' access to genome editing. The point is that the last generation could always have more advantages than the previous ones, because it could have access to better interventions. This means there could always be a gap (at the level of opportunity)[7] between one generation and the next: the one coming later could always be superior because the "eldest" one will never be able to compete.

We have already explained that for some prospective parents it will become easier to have a biological child with reproductive techniques like cloning, parthenogenesis, artificial womb and the production of artificial of gametes. Even people who do not have egg cells or sperm, or whose gametes present genetic anomalies, could have a child with their own DNA, because they could use their own somatic cells, or turn to gametes without anomalies. At the same time, we must also be aware that introducing new reproductive technologies may negatively affect our 'reproductive freedom'. In general, those who defend technologies intervening on the human genome state that the current eugenics

[6] *A US Drugmaker Offers to Cure Rare Blindness for 850.000 Dollars*, 3 January 2018, https://www.cnbc.com/2018/01/03/spark-therapeutics-luxturna-gene-therapy-will-cost-about-850000.html, R. Lewis, *What should gene therapy cost?*, 26 ottobre 2017, blogs.plos.org/dnascience/2017/10/26/what-should-gene-therapy-cost/.

[7] R. Sparrow, *Enhancement and Obsolescence: Avoiding an "Enhanced Rat Race*", "The Kennedy Institute of Ethics Journal", 25(3), 2015, pp. 231–260; K. Hutchison, R. Sparrow, *What Pacemakers Can Teach Us about the Ethics of Maintaining Artificial Organs*, "Hastings Center Report", 46 (6), 2016, pp. 14-24.

plan is different from the past totalitarian one, because the aim now is only to defend rather than restrain reproductive freedom. The new eugenics start from the idea that the parents' freedom of choice constitutes the best antidote against the danger of state coercive policies.[8] But despite the value we recognise in reproductive freedom in our society[9], with the arrival of genome editing, correcting the unborn child's DNA may seem the most reasonable and moral thing for a future parent to do. Indeed, intervention to correct the genetic code could be relatively simple: and the result would of course be that the embryo would come into the world without anomalies which could then condition its life quality and, unlike pre-implantation diagnosis no embryo would be abandoned or destroyed. Of course, in the case of serious genetic anomalies, most people wishing to have a child would ask for an intervention on their embryo's genome. But some people could react differently and not accept genome editing: they may have negative prejudice towards technology in general or think that modifying the genetic code of a human embryo is wrong because it constitutes unacceptable interference in natural processes or divine providence. Yet, at the time of genome editing, what will we do in this case? Will we leave to the parents the right to choose whether to correct their embryo? Or will health operators be obliged by law to practise editing intervention, even if the parents don't give consent or their willingness is against? And this could apply to not only therapeutic, but also enhancement interventions: that is, to every treatment designed to improve the genetic heritage. As Stefan Sorgner explains, it is not true that genetic enhancement produces more irreversible consequences, or limits personal autonomy any more than upbringing, that it destroys relationships or is less necessary than upbringing. However, as Sorgner warns, if we assume that upbringing and genetic changes are analogous processes, why should a 'liberal' state consider upbringing obligatory but leave the gene therapy or enhancement to their parents?

[8] C. Mills, *Reproductive Autonomy as Self-Making: Procreative Liberty and the Practice of Ethical Subjectivity*, "Journal of Medicine and Philosophy", 38, 2013, pp. 639-656, p. 640.

[9] As John Harris writes: "The best way to avoid totalitarism, and avoid the risk that individual or social prejudice imposes what type of children people should have, is to allow the parents to be free in this area to make the choice they consider most right. (...) Because it is probable that there will in most cases be as many choices as there are people", J. Harris, *Rights and Reproductive Choice*, in J. Harris, S. Holm (a cura di), *The Future of Human Reproduction: Ethics, Choice and Regulation*, Clarendon 1998, p. 22.

It could be said that even if we had the legal obligation to correct the unborn child's genome, this would not imply serious limitation of reproductive autonomy. Indeed, parents always have the duty to protect the interests of their child and ensure them with the best therapeutic treatment available. However, with the introduction of genome editing techniques, limitation on prospective parents' reproductive freedom could be 'unprecedented', because a parent may be obliged not only to correct possible embryo anomalies, but also to give up sexual in favour of assisted reproduction. Indeed, intervention to correct the embryo's genome would probably be much easier if the embryo were conceived in vitro, because it would not be necessary to go through the woman's body in order to modify it. Diagnostic and later therapeutic intervention could, then, be practised at once, at the moment of conception or immediately after the first cell divisions. But if the embryo were produced sexually, genetic editing could only be performed in an advanced phase of embryo development, because many days could go by before the pregnancy is discovered by the woman. For this reason, if fertilisation occurred with an assisted reproduction, genome editing may be practised on the embryo of a cell (zygote) or on blastomeres. By contrast, if reproduction goes through a sexual relationship, the germline genome editing would have to be practised on an multicell embryo: the risk of error would, then, be greater, as would the probability that some cells of the embryo do not receive the desired genetic modification. This is why, with IVF, there would be greater probability of preventing diseases' transmission and furthering the unborn child's well-being.

Once the assisted reproduction intervention has been practised and after the genome correcting intervention has been completed, the embryo must be transferred into the woman's uterus, where it will continue its development. However, with the development of reproductive technologies allowing one to carry on the embryo's growth outside the human body in an artificial uterus, will women still be able to choose to have a child through pregnancy? At the moment, a person's birth may only occur through pregnancy: and there are not yet technologies able to substitute a woman's body. But with the technological development, our ability to bring up an embryo outside the human body could improve. Maybe also tomorrow the human body will be the safest place to be born and grow: but let us hypothesise that in the future the artificial uterus becomes safer than the human body. Besides, an artificial uterus could permit monitoring of the embryo's condition twenty four hours a day and consequently give the possibility of recording problems or anomalies in the embryo's development in

real time. Further, an artificial uterus would never be subject to unavoidable accidents, injury and aggression and still be a more aseptic environment. Then, think at the lifestyle and habits that can damage an embryo: what will happen if one day the artificial uterus becomes reality? Will those women who prefer to carry on pregnancy considered morally irresponsible? These women could strike many as selfish and thoughtless, because they would rather live the pregnancy than care about the unborn child.

It is true that things in the future may turn out differently from how we imagine. But today, women who choose to have a child are often criticised if at the moment of conception, pregnancy and birth they think also of their interests.[10] Many people expect the pregnant woman to undergo invasive interventions to allow the condition of the embryo's health to be monitored regularly. The idea is that the more interventions the woman agrees to undergo, the easier it is to recognise possible problems or anomalies in the embryo. Further, it is often maintained that birth should occur in hospital and women who choose labour and birth at home or in a maternity home put their own interests before the unborn child's: so they are bad mothers. Why should we think that this attitude to women will change at the very moment when we will use such technologies as genome editing or an artificial womb? We cannot write off this problem as something not so important: in fact, secular and religious bioethics largely converge on woman's moral responsibility. religious bioethics always condemn the interruption of pregnancy, while secular bioethics recognise the woman's right to choose; but once the woman has chosen to continue her pregnancy, bioethics thinking largely converges that at that point, the pregnant woman must no longer think of her own interests, but only worry about the unborn (or future) child's.[11]

In conclusion, new reproductive technologies open original scenarios which may substantially broaden future generations' reproductive freedom. But at the same time, the development of these technologies may not only limit people's autonomy, but also make current social injustice more and more acute. It is important to start reflecting on these problems to reduce the danger that scientific and technological innovations only benefit very few people. We must

[10] F. Wolland, L. Porter, *Breastfeeding and Defeasible Duties to Benefit*, "Journal of Medical Ethics", 2017, 43, 8, pp. 515-518; F. Simonstein, *Gene Editing, Enhancing and Women's Role*, "Science and Engineering Ethics", February 2017, DOI: 10.1007/s11948-017-9875-5

[11] C. Botti, *Madri cattive: una riflessione su bioetica e gravidanza*, Il Saggiatore 2007.

also think about the responsibilities we have towards future generations and how fair it is to balance their interests with our own interests. Demanding that once pregnancy has been chosen, the woman sacrifice all her interests and well-being for the unborn child's well-being is unfair. Finally, we should perhaps reflect on the world we want to leave to those generations and persons living after us, in that the choices we make today will affect the world there will be tomorrow. Allowing future generations to access the new reproductive technologies must be important, just as it is important to prevent the transmission of very dangerous diseases. But at the same time, we should assess how our efforts could be of benefit to the population and contribute more efficiently to overcoming social injustice.