CORRESPONDENCE

WILEY PRENATAL **DIAGNOSIS**

Comment on "Should gene editing replace embryo selection following PGD? Some comments on the debate held by the International Society for Prenatal Diagnosis"

We have recently read the article entitled "Gene Editing Should Replace Embryo Selection Following PGD," recently published (26 April) in *Prenatal Diagnosis*.[1] It corresponds to the debate held in the 22nd annual meeting of the International Society for Prenatal Diagnosis held in 2018. However, our final thoughts about the discussion and the subsequent article are somewhat mixed, since they offered appreciable arguments on the issues at stake, but also substantial issues and gaps that deserve comments. This paper is aimed at introducing an alternative and four deep nuances to what the experts stated.

The alternative, nevertheless, can be summarized quite easily: it might happen that the proposed crossroad is not inevitable. Indeed, it might perfectly happen that both techniques coexist in the near future. PGD might continue to be the standard response to all those couples who are willing to prevent monogenic disease, at least for the time being. Instead, gene editing (GE) could be used to reach those aims that can hardly be attained via embryo selection following PGD, such as a general improvement in the genes of the embryos, which substantially reduces the risks of postnatally suffering from serious pathologies.[2]

The first nuance has to do with the question of risk. As the moderator rightly asserted, it is impossible to raise seriously the question of whether GE can replace PGD at the present moment. Our poor control of GE and the substantial risks involved make the negative answer obvious.[3] Therefore, the debate must be directed towards a future in which these technical issues have been resolved. However, if this is the starting hypothesis, then the allusions made by J. R. Vermeesch to the risk inherent in the technique lose all sense. The same applies to his claims that we will never be able to avoid using PGD because GE will never be safe enough. If risk factors are to be included in the debate, then it should be underlined that we are not certain at all about the safety of PGD. To begin with, PGD entails embryonic cell biopsy, a circumstance that sometimes causes the loss of the embryo. Furthermore, we are more or less sure that PGD is clinically safe at birth, but this is still unclear in older individuals born via PGD. Indeed, according to animal studies, this might not be the case.[4] Therefore, if we are to ban a technology on the basis of its possible risk, then PGD should also be banned. So, one must conclude that allusions to risk should have been avoided both because they depart from the agreed hypothesis—in the future, GE techniques will be improved and will be acceptably safe—and because they assume the impossible: to be able to guess what the course of events will be.

Our second concern has to do with an issue that somehow went unnoticed. It is true that the first participant (Dagan Wells), who defends the FOR position, shows correctly that GE allows for a reduction in the number of surplus embryos in assisted reproduction techniques. However, to our astonishment, what he does not say is that this is not the only point at which GE is far more morally acceptable than PGD followed by embryo selection. In fact, Wells overlooks a crucial conceptual issue that differentiates the two techniques. In fact, GE is intended to safeguard the health of offspring who may be suffering from various pathologies through genetic modifications. Therefore, it constitutes a therapeutic action, free of any moral suspicion. Embryo selection, instead, can only be considered a therapeutic action for perspective parents who suffer from the impossibility of generating biologically healthy offspring. Indeed, detractors of genetic selection argue that this technology contains an aroma of eugenics.[5] In fact, what the technique involves is not to "cure"[6] embryos but simply to choose which embryos will be transferred. Therefore, considering that both techniques—GE and PGD—are similar is a blurred statement for an ethical discussion.

Thirdly, it is quite striking that the participants in the discussion accept that the scope of GE is limited to a few concrete circumstances similar to those that justify the use of PGD. This statement completely dismisses the possibilities that GE offers in practice. PGD followed by embryo selection and GE share a common use: they can both be employed to efficiently prevent monogenic diseases prenatally. However, GE promises much wider applications.[7] Ideally, GE could allow for correcting multiple genes of an embryo, which would go far beyond preventing the birth of children affected by a monogenic disease. For instance, GE could give our offspring an expression of genes more suited to reducing their predisposition to cancer or to improving their immune system's performance. While this may not seem easy to implement right now, it cannot be ruled out that the situation will change dramatically in the future. What is undeniable in any case is that this kind of substantial improvement will only be possible, thanks to the use of GE techniques. Therefore, it is uncertain whether PGD and GE possess a similar capacity in purely scientific terms. Indeed, GE is far more versatile than PGD followed by embryo selection. Thus, it will be exponentially superior, if we are effectively capable of acquiring sufficient knowledge about

the human genome to understand what changes are satisfactory for human beings.

J. R. Vermeesch could reply to our comment by saying that we are talking about enhancement, not therapy. Indeed, this is quite probable, since he apparently assumes that only those interventions aimed at curing monogenic diseases in embryos can be considered as therapeutic. However, medicine is increasingly seen as a global intervention that is aimed not only at curing but also at preventing diseases. Moreover, we must remember that GE that alters a gene that triggers a monogenic disease is not curative since that embryo does not suffer from the disease. It is therefore clearly preventative not curative. Therefore, if this type of GE is morally acceptable, then GE for preventive purposes should also be acceptable. Both behaviours are equally therapeutic.

What would happen in cases where the intervention is aimed at improving the immune system? In our opinion, we would also have to think of these activities as therapeutic actions.[8] This is due to the evidence drawn from some of the interventions aimed at purposes that have little to do with the cure of illnesses and which, nevertheless, are described as therapeutic. The best example of this is vaccines. Vaccines do not cure any disease. They do not even diminish our predisposition to suffer from them: they improve our response to them. However, this improvement is not usually considered a form of enhancement but a form of therapy. So, why should not we think in the same way about GE?[9] If this is the case, we must conclude that the therapeutic use of GE extends far beyond the cure of a disease. But then it is entirely possible to maintain the therapy/enhancement distinction in GE and thereby avoid the slippery slope effect and thereby avoid the slippery slope effect that the rapporteur describes as almost inevitable.

Moreover, it is important to emphasize that even if we do not accept our main argument—that is, if we consider the use of GE for preventive purposes or to improve the immune system as enhancement—it would still be possible to draw distinctions between enhancement that affects absolute goods, such as health and enhancement that affects positional goods, such as intelligence. From this distinction, it would also be possible to draw a barrier between what is permissible and what is not. Of course, this does not necessarily mean that this barrier would not go unchallenged on a regular basis. However, this also happens in the context of PGD, where evidence shows some questionable uses of this technique.[10]

The reader should not think that the conclusion of everything we have argued in this text is necessarily that GE should replace PGD followed by embryo selection. Our purpose has not been to answer this question. What we have tried to do is to clarify that the original discussion suffered from some issues and gaps, which our contribution may have helped to clarify. Obviously, there are a lot of moral arguments against GE that we have not dealt with here. The readers may well consider them when deciding his or her answer to the question posed. But at least now they can do so knowing that(a) the risk argument should not be seriously taken into account if we think about the future, (b) PGD followed by embryo selection and GE are conceptually different (eugenics/therapy), (c) GE can potentially give us far superior options to the alternative, and (d) the use of GE to prevent or improve our response to specific pathologies does not definitely constitute enhancement or, even if it were to, this would not mean that it could not be distinguished from other forms of enhancement.

DATA AVAILABILITY STATEMENT

Not applicable.

CONFLICT OF INTEREST

Both authors declare no conflict of interest at all.

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