Viewpoint

Human embryo genome editing and child health

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In recent years, new molecular tools have been developed which make it possible to modify the structure of DNA relatively easily. Indeed, the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) system associated with a guide RNA sequence and an endonuclease (Cas9) makes it possible to target very precisely any sequence of the molecule and to cut the DNA strands in order to remove or replace the target fragment or to insert a new DNA sequence. The technique described in 2012 by the teams of Emmanuelle Charpentier and Jennifer Doudna [1] is used for many experimental works on plant, animal and human cells and has led to the development of similar processes capable of improving its performance.

The potential medical applications of CRISPR-Cas9 have been rapidly considered either to correct mutations in case of monogenic disease (somatic gene therapy) or in oncology (immunotherapy). The first clinical trials should be initiated in China and the USA in 2017. In this context, there was considerable agitation in the scientific community in the spring of 2015 when a team of Chinese researchers published the results of their work using CRISPR-Cas9 to modify a gene in human embryos [2]. The results of the experiment on triploid embryos, therefore unsustainable, were not very conclusive but the reactions were strong. Indeed, regardless of the comments concerning the effectiveness and safety of the method, the risk that it could be used to meet trivial or eugenic aspirations has been advanced as is regularly the case when a new technique capable to interfere with human procreation is developed. Without dwelling on the comments highlighting the desire to create designed children, which are more based on fantasies than on a really conceivable perspective, and which ultimately prevent any serious debate, perhaps it is useful to question on the scientific and ethical issues raised by medical interventions aimed at modifying the genome of an embryo.

The most obvious indication, and probably the only one, would be to avoid transmission to the child of a genetic alteration responsible for a particularly serious disease. This is currently possible through prenatal diagnosis (PND) or preimplantation genetic diagnosis (PGD). This is why it is often asserted that there would be no medical reason to seek to modify the genome of an embryo. There are, however, some exceptional cases where PND and PGD cannot meet parents' wish for a healthy child, for example when one of the two partners is homozygous for an autosomal dominant alteration such as Huntington's chorea or when both partners are homozygous carriers of autosomal recessive alterations such as those responsible for cystic fibrosis. Would it then be possible to correct the deficient gene by intervening on the embryo? The molecular tool CRISPR-Cas9 has been used on embryos at the stage of the first cell in many species to create animals of which one or more genes are modified (see review in [3]). However, the results were far from perfect because a greater or lesser proportion of the animals that are born were not carriers of the desired modification and it was not certain that the intervention did not induce undesired effects. This is not crucial when it comes to experimental work where animals lacking the desired criteria can be eliminated. This would be unthinkable in the human species without testing the efficacy and safety of the method on the embryos prior to their transfer to the uterus.

Another route of approach would be to edit the germ cells genes before fertilization. This could satisfy those who on principle refuse any intervention or research on the human embryo. But it should not be ignored that any action modifying the genes of gametes would require, at least during the period of development of the techniques, to create embryos which should be analyzed to ensure that there is no deleterious effect for the child. This creation of human embryos for research is forbidden in many countries including France.

Another situation that could be considered is PGD failure. Indeed, it may happen that the embryos that could be transferred to the uterus are not suitable, because they are all carriers of the genetic anomaly that is sought to be avoided. It is not unusual for the couples concerned to ask whether the affected embryos could not be "treated" rather than destroyed. Would it be unacceptable to correct the embryo genetic alteration of which it is a carrier, rather than destroy it, to lead to the birth of a healthy child? In its reflection, the INSERM ethics committee considered that a research could be made to the potential benefit of the embryo when it was part of a parental project [4]. This type of research, which has been provided for in the Public Health Code since 2016, has been confirmed as acceptable by the French Constitutional Council, which considers that research can "prevent or treat pathologies in the embryo" [5].

Could it be possible that the "treatments" go so far as to edit an altered gene of the embryo, as it is commonly accepted in children or adults? The question deserves to be asked, but is far from being resolved whether for scientific, regulatory or ethical reasons.

All experiments up to now in the animal have consisted in modifying the genome at the zygote stage, i.e. in the first cell of the embryo, and have not always been effective as indicated above. But an embryo that has been the object of a PGD consists of eight cells or more, and currently there is no technique to modify its genome effectively at this stage.

On the regulatory front, French legislation and the Oviedo Convention, which has been ratified by many countries, stipulate that "an intervention aimed at modifying the human genome can only be undertaken […] not to introduce a change in the genome of the offspring". It would therefore be necessary to change the regulations in order to modify a gene in an embryo intended to start a pregnancy.

There remains the fundamental ethical question concerning the legitimacy of an act which would result in a modification of the genome in all the cells of the future individual and which would therefore be transmissible to subsequent generations. Since 1975 and the Asilomar conference, there has been a consensus (not clearly stated) in the scientific community that this is a threshold that cannot be crossed. This position deserves to be reconsidered, however, by integrating the potential new possibilities opened up by the development of CRISPR-Cas9 and other similar methods into a reflection on all the medical acts involved in human procreation and which have the effect of influencing the genetic constitution of children to be born. Not to mention PGDs commonly practiced in some countries to choose the sex of the child, this reflection should concern the genetic criteria taken into account in the procreation with spermatozoa or oocytes, the embryonic reconstructions associating the enucleated cytoplasm of a donor oocyte and the nuclear genome of the future parents [6] or making in vitro fertilization by ICSI (IVF-ICSI) with the spermatozoa of sterile men who are known to carry genetic alterations. It is common practice, for example, to practice IVF-ICSI with spermatozoa of sterile men carrying a mutation of the gene responsible for cystic fibrosis or a micro-deletion of the Y chromosome. In this last case the consequence of the medical intervention is the transmission of genetic alterations to the offspring which could not have been transmitted naturally.

Should we therefore exclude any action likely to edit the genome of a human embryo? Yes, certainly, if the embryo is part of a parental project. It would indeed be inconceivable to do so in the present state of scientific knowledge. In addition, there should be an in-depth debate on the ethical and social issues and consequences of this new form of medical intervention. On the other hand, the answer is certainly No, when it is for research purposes. CRISPR-Cas9 and other similar techniques are extraordinary molecular tools that should improve knowledge about embryonic development and its dysfunctions. This was confirmed by the World Summit on the subject convened by the American Academies of Science and Medicine in December 2015 [7], and by the research institutions of the United Kingdom [8] and the French National Academy of Medicine [3].

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