Mitochondria replacement in cases of serious diseases – ethical aspects 2013:2

Summary of a report

The Swedish National Council on Medical Ethics
Summary of the original report "Mitokondriebyte vid allvarlig sjukdom – etiska aspekter, 2013:2" published in November 2013.

Foreword

The Swedish National Council on Medical Ethics has on its own initiative written this report on the ethical aspects of mitochondria replacement. The aim of the report is to encourage a debate in society and to provide support for future considerations on regulations.

Mitochondria replacement was a current issue for the Swedish National Council on Medical Ethics as early as 2002, when the Council held a seminar on the technique at the Riksdag (The Swedish parliament), together with the Swedish Research Council working group on research ethics at the Scientific Council for Medicine and Health.

In light of new progress in research and the fact that the United Kingdom has for several years been considering permitting mitochondria replacement, the Council decided in 2012 to summarise its discussions in a report. The prevention of mitochondrial disease using this method was also highlighted in the Council's report entitled *Assisted reproduction – ethical aspects 2013:1*, under the chapter 'The future'. This issue was initially part of the project about assisted fertilisation, but it subsequently became the subject of a separate report.

This report was produced by a working party within the Council comprising Council members Sven-Olov Edvinsson, Chatrine Pålsson Ahlgren, Elina Linna and Barbro Westerholm. Also part of the working group were Göran Hermerén and Nils-Eric Sahlin, both experts at the Council. At the Councils' secretariat, Lotta Eriksson acted as project manager for the work and together with Karin Wilbe-Ramsay, research officer, prepared the manuscript based on discussions held in the working party and in the Council.

The decision to publish this report was taken by the following Council members: Kjell Asplund (chair), Chatrine Pålsson Ahlgren, Helena Bouveng, Sven-Olov Edvinsson, Anders Henriksson, Elina Linna, Barbro Westerholm and Anders Åkesson. Also involved in the preparation of the report were: Lars Berge-Kleber, Emil Bergschöld, Ingemar Engström, Martin Färnsten, Göran Hermerén, Åsa Nilsonne, Sineva Ribeiro, Nils-Eric Sahlin and Elisabet Wennlund, all experts at the Council.

Over the course of the project, the Council listened to the views of a number of experts (see Annex 1). As part of this work, an open seminar was also held on 17 May 2013 at Rosenbad Conference

Centre for a dialogue with experts, specially invited guests and interested members of the public.

The medical facts in the report have been reviewed by MD Martin Engvall and MD Karin Naess, at the Centre for Inherited Metabolic Diseases at Karolinska University Hospital, and Charles Hanson, associate professor in reproductive genetics at Sahlgrenska University Hospital. The report was also reviewed by Elisabeth Wallenius, president of the National Alliance for Rare Diseases Sweden.

Stockholm, November 2013

Kjell Asplund

Key conclusions

In light of the current uncertainty concerning the medical risks, the Council does not consider that the technique of mitochondria replacement is ethically acceptable. The need for mitochondria replacement must be weighed against the fact that the scientific knowledge is so fragile. There are currently other courses of action, i.e. other possibilities of having children without a predisposition to mitochondrial disease, which the Council has considered in its assessment.

A majority of the Council members consider that the technique may be ethically acceptable per se, provided that it can be done in a safe manner and the medical risks and effects in both the short and long term are deemed acceptable.

A minority of the Council members consider that the technique per se is not ethically defensible. They believe that allowing the genetic modification of reproductive cells in the future would mean too great a risk of undesirable developments and consequences. The minority thus stand by the ban in principle on genetic modification of human reproductive cells.

The Council is in agreement that scientific developments in the area should be followed. There should be a broad debate in society about gene therapy for the purpose of preventing serious illnesses. This report could provide input into such a debate.

Background

Some families are seriously affected by hereditary diseases. In some cases, these diseases are caused by inherited damage in the mitochondria, the cells' energy producers. The lack of energy – which can affect most of the body's organs – leads to serious diseases. Patients with the most serious conditions die in early childhood. Other disorders cause symptoms later in childhood or in early adulthood. In these cases, they can cause increasingly severe damage to muscles, brain, nerves, liver, blood or eyes.

Mitochondria replacement is a technique under development which involves the damaged DNA in the mitochondria being replaced with healthy mitochondrial DNA in connection with assisted fertilisation. The issue is a matter of principle as the technique involves altering the DNA in a reproductive cell or fertilised egg. This has previously been considered unacceptable and is forbidden in Sweden under the Genetic Integrity Act (2006:351). If this technique were to be allowed, it would only be used on a few individuals per year.

Mitochondria replacement could subsequently mean that we prevent children from being born with these serious diseases. The method could also drastically reduce the risk of future generations being affected by such disease.

In research studies, mitochondria replacement has been carried out on animals, as well as unfertilised and fertilised human eggs. As yet no child has been conceived using the technique. The knowledge base is therefore limited and it is difficult to predict the short-term and long-term risks if the technique were brought into clinical use.

Ethical aspects

The Council has discussed and analysed the issue on the basis of two main problems. The first concerns the scientific knowledge: do we know enough about risk uncertainties for the individual and future generations for mitochondria replacement carried out on humans to be ethically acceptable? The other problem is whether it is morally justifiable to make changes to inherited mitochondrial DNA in order to prevent mitochondrial disease.

Mitochondria replacement raises the ethical conflict between, on the one hand:

- the interest of the prospective child being free from disease and serious suffering,
- the interest of the parents having healthy children, and
- the interest of the parents having children who are genetically related to them;

and on the other hand:

- the requirement of respect for human dignity and a humanistic view of the individual,
- concern for the possible consequences that use of the technique could have on society in the long term, and
- uncertainty concerning potential medical risks for the prospective child.

Overview of the arguments for and against the technique

Arguments that can be made in favour

- It will be possible to prevent serious disease in children.
- Women carrying mutations in their mitochondrial DNA can be given the opportunity to have their own children with a dramatically reduced risk of mitochondrial disease.
- The predisposition to these illnesses could possibly be prevented in coming generations as well.
- Research and development of the technique can provide valuable new knowledge.

Arguments that can be made against

- The method could represent a threat to human dignity and the humanistic view of the individual.
- There are knowledge gaps concerning the medical risks for the prospective child and future generations.
- The technique could have other unpredictable and undesired consequences.
- There are alternative courses of action that are acceptable.

Reflections and viewpoints

Decisions, risks and knowledge gaps

The scientific base for assessing the risks of mitochondria replacement is currently very limited. In light of the current knowledge gaps, the Council considers that it is not ethically acceptable to use the technique in clinical trials on humans, i.e. to implant a fertilised egg that has been subject to mitochondria replacement into the womb.

Actors: the child and the parents

From the perspective of the prospective child, there are strong arguments to be made in favour of mitochondria replacement, as it can allow the prevention of severe illness, suffering and possibly premature death. In the Council's view, this has greater weight than the idea that this type of technique would jeopardise the prospective individual's integrity. The Council does not consider that mitochondria replacement would pose a threat to the individual's integrity.

How the child feels about his or her conception will probably largely depend on how and when the child is informed about his or her conception. As mitochondrial DNA is inherited from the maternal line and is used in investigations of kinship, it is important that the child is informed at a sufficient stage of maturity that he or she was conceived using tissue donation, which means that the child's mitochondrial DNA is different to that of his or her mother's. Mitochondria replacement also means that the probability of future generations carrying the damaged mitochondrial DNA will decrease, which is also an advantage for the prospective child if it is a girl, as she will be able, as an adult, to fall pregnant and be less worried about having a seriously ill child.

From the parents' perspective, there are strong arguments in favour of allowing the technique. However, the Council wishes to stress that there are alternative courses of action for couples where the woman is a carrier of mutated mitochondrial DNA to have children, such as egg donation or adoption.

When it comes to the individuals and families affected, the Council understands that they may have a strong desire to have children who are genetically related to them and do not have the

predisposition for mitochondrial disease. But the Council considers that the current advantages of the method do not on the whole outweigh the potential risks of the new technique.

Alternative courses of action

The Council considers that egg donation and adoption can be seen as possible alternatives for some of the families that run a considerable risk of having a child that is affected by serious mitochondrial disease. What is to be considered an alternative is, however, dependent on several factors, such as the plans, goals, values and ideals of the prospective parents. Some have a strong desire to have a child with whom they have a genetic link, others are less or not at all concerned about there being a genetic connection. The prospective parents must form their own view of the various alternative courses of action, without pressure. But it is the obligation of society to inform them of the options available and to decide which of these should be offered under public health care.

The health and medical care services should provide family planning information in a careful and responsive manner, taking into consideration the individual's knowledge, goals and values. Information about the different ways of having children without a predisposition to illness or with a lesser risk of illness should be provided in a neutral and non-influential way.

The Council does not consider that prenatal diagnosis can be seen as an alternative to mitochondria replacement. This is a diagnostic method that can, in some cases, provide the expectant mother with greater knowledge about the foetus. However, diagnostic results that are inconclusive or difficult to interpret can mean that the pregnant woman is confronted with the difficult choice of whether to continue with or terminate the pregnancy.

Preimplantation genetic diagnosis (PGD) can, in some cases, reduce the probability of mitochondrial disease. However, it cannot be ruled out that fertilised eggs that have been diagnosed carry pathogenic mitochondrial DNA. From this point of view therefore, PGD is currently not a reliable alternative for parents wanting to avoid serious illness in their child.

Aspects that concern society

Mitochondria replacement is a form of gene therapy that can be clearly distinguished from other forms of gene therapy as the technique involves changes only to the mitochondrial DNA and not to the nuclear DNA. This demarcation is clear.

The Council considers that a donation of mitochondrial DNA from an unfertilised or fertilised egg is not on a par with a normal egg donation (or donation of a fertilised egg) and should instead be regarded as a kind of tissue donation.

The Council considers that children conceived using this method have two genetic parents, not three, as is sometimes claimed in various media. The Council does not consider that the method per se represents a threat to our view of the individual and human dignity, that is to say the concept of the equal value of all people in the sense of people having equal rights. Preventing serious illness at the fertilisation stage is not discriminatory against people who already suffer from such illnesses.

In numerous previous positions, the Council has also supported research on fertilised eggs and the use of tissue from them to produce stem cells. Consequently, mitochondria replacement does not amount to a violation of human dignity in the meaning to which the Council has already subscribed.

However, it is important to be alert as to how these new techniques could affect patient groups and people with a predisposition to serious hereditary illnesses. Women with a predisposition to mitochondrial disease may feel under pressure to use the technique, or other courses of actions, when planning to start a family. Disability interest groups have differing views of PGD to prevent serious hereditary illness. It is possible that there will be varying views on mitochondria replacement as well.

Divided positions

The Council has not been able to reach a unanimous position on whether mitochondria replacement is ethically acceptable in terms of principles/morals, provided that the technique is developed in such a way that the medical risks and effects involved are acceptable for the prospective child and future generations. This applies above all to the arguments concerning the slippery slope, the future

consequences and the extent to which the technique represents a future threat to the humanistic view of the individual and human dignity.

A majority of the Council's members consider that modifying mitochondrial DNA can be ethically acceptable per se, provided that the technique is developed in such a way that the medical risks and effects are acceptable for the prospective child and future generations.

A majority of members also consider that with clear regulation it would be possible to prevent a development that is not desirable. Mitochondria replacement as a technique can be clearly defined as a special form of germ line therapy that affects the individual's genetic make-up only to a limited extent. Moreover, the majority consider that the next steps can be clearly defined. It is therefore possible to design a regulation that would prevent undesirable developments.

In some respects the method can be compared to PGD and PGD/HLA, which are currently subject to strict regulations. PGD is only permitted in cases of very serious hereditary illness, and PGD/HLA is only permitted after special consideration. By using strict regulations for mitochondria replacement, it should be possible to avoid the extension of clinical indications in a development towards further use of gene therapy in order to refine human beings. A clear prohibition against altering the human genome for other reasons than preventing illness would prevent developments of a eugenic nature.

A minority of the Council's members consider that modifying mitochondrial DNA is not ethically acceptable per se, regardless of whether or not the technique has been developed in such a way that the medical risks and effects are inconsiderable for the prospective child and future generations. Permitting this limited form of gene therapy would mean permitting something that has previously been considered unacceptable, which means crossing a line of principle, i.e. the ban on genetic modification of humans.

A minority of members consider that altering the DNA of a prospective individual to prevent illness is much too far-reaching an act. Although mitochondria replacement is a limited form of gene therapy that can be clearly defined, permitting this technique could pave the way for developments that are difficult to control and predict, and that may cause future problems with regard to setting out clear boundaries. Allowing this technique could pave

the way for the modification of less serious conditions and for choice of qualities, which taken as a whole could foster the concept of the perfect human. In the long run, this could be a threat to the humanistic view of the individual and human dignity. If this technique is permitted, we would thus risk a development towards a society that discriminates, a society that places demands on citizens to reject and make the right choices, a society that becomes more technified and where what we consider makes us human is lost.

Annex 1:List of experts whose views have been sought

List of external experts whose views the Council has heard in the course of its work on this report. The experts listed below attended an internal Council meeting and/or the open seminar on 17 May entitled *Mitochondria replacement for the prevention of mitochondrial DNA disorders – from research to clinical use*, at Rosenbad Conference Centre.

Christoph Freyer, MD, molecular biologist, Centre for Inherited Metabolic Diseases, Karolinska University Hospital

Martin Engvall, MD, Centre for Inherited Metabolic Diseases, Karolinska University Hospital

Outi Hovatta, MD, professor of obstetrics and gynaecology, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, consultant physician, Karolinska University Hospital

Erik Iwarsson, MD, associate professor in clinical genetics, Department of Clinical Genetics, Karolinska University Hospital

Karin Naess, MD, Centre for Inherited Metabolic Diseases, Karolinska University Hospital

Elisabeth Rynning, Justice of the Supreme Administrative Court, former professor of medical law

Göran Solders, MD, associate professor, Department of Neuorology and Department of Neurophysiology, Karolinska University Hospital

Juliet Tizzard, Head of Policy and Communications, Human Fertilisation and Embryology Authority

Hugh Whittall, Director, Nuffield Council on Bioethics