Executive summary

Health Council of the Netherlands. Nuclear transplantation in cases of mutations in mitochondrial DNA. The Hague: Health Council of the Netherlands, 2001; publication no. 2001/07.

Mitochondria are intracellular organelles that are essential for the supply of energy to the cells. Located in the mitochondria are a small number of genes, which are inherited via a maternal line. Children inherit the mitochondrial genes exclusively from their mother and daughters transmit these genes to all of their children.

Mutations in mitochondrial genes can lead to a wide variety of disorders, such as myopathy, blindness or diabetes. The severity of these disorders partly depends on the ratio between the quantities of mutated and normal DNA in the mitochondria. Because this ratio can change radically from one generation to the next, it is in many cases not possible to predict the seriousness of the disease in children of affected mothers. Life expectancy is also partly dependent on this ratio. There is usually no treatment for this condition and in some mitochondrial disorders, life expectancy does not extend beyond childhood.

In theory, a technique is available that would allow couples in which the woman has a mutation in her mitochondrial DNA, to have a healthy child “of their own” if they so wish. A cell nucleus can be retrieved from one of the affected woman’s oocytes and inserted into a donor oocyte from which the original cell nucleus has been removed. Then in vitro fertilization is performed. This procedure is a form of nuclear transplantation referred to in the literature as “in vitro ovum nuclear transplantation” (IVONT). Variants of this transplantation technique are possible in which the nucleus is transferred to an enucleated donor oocyte after fertilization. These procedures result in an embryo which inherits the majority of its genetic characteristics from the mother and father, plus a small proportion from the donor (via the mitochondrial DNA).

Because the resultant genetic modification is not only passed to the child, but possibly also to a subsequent generation, IVONT and other similar techniques are to be regarded as forms of germ-line modification. The current level of knowledge is insufficient to provide a definitive answer as to the safety of these techniques. Because germ-line modification is accomplished via a nuclear transplantation, the risks would appear to be considerably lower than those associated with forms of (germ-line) gene therapy in which a gene or part of a gene is introduced with the aid of vectors. It is not sufficiently clear, however, whether or not the removal and introduction of the cell nucleus adversely affects the further development of the oocyte. It is also possible that the chromosomal and mitochondrial genes may in some way be incompatible. Research into various aspects of nuclear transplantation in cell lines and experimental animals has not revealed any harmful consequences, but such studies have been limited in extent. Further research into the safety of the method is needed in order to establish whether such clinical intervention is justifiable.

The techniques in question (and the associated research) are satisfying an important need. It concerns the opportunity to offer assisted reproduction techniques to couples who will otherwise not be able to have a genetic child of their own that does not carry the woman's pathogenic gene defect. This benefit has to be weighed against possible ethical objections. The question of the acceptability of this technique and its application can in some respects be said to put a different complexion on the relationship between various topical issues – such as germ-line modification, cloning, embryo research and assisted reproduction. Here we must not only consider the interests of the individuals concerned (the couples seeking help, the children that will come into the world by means of nuclear transplantation and the oocyte donor), but also those of society as a whole. The "slippery slope" argument is one aspect that warrants closer consideration.

The recent Bill on the Use of Gametes and Embryos offers some scope for the use of nuclear transplantation in preventing mitochondrial disorders in offspring. It contains a ban on germ-line modification, but this relates exclusively to the alteration of the genetic material in the nucleus of germ-line cells – something which categorically does not occur with nuclear transplantation. The Bill does, however, contain a ban on reproductive cloning. Depending on how it is interpreted, that ban does have implications for the application of one particular variant of the technique discussed in this advisory report. The ban on creating embryos exclusively for research purposes means that, for the present, no preclinical research into the efficacy and safety of nuclear transplantation can be performed with human embryos – "for the present" because the Bill provides for the reconsideration of this ban after a minimum of three years. Whether such research will indeed be possible subsequently depends on how the relevant section of the Act is interpreted. Finally, a central review of

preclinical and clinical research into the techniques discussed in this advisory report is only required in so far as it involves embryo research, according to the Bill. Depending on the chosen method of nuclear transplantation, it is possible that important components of the ensuing research will not be classified as embryo research. In that case, such components would possibly not need to be submitted to the Central Committee for Medical Research Involving Human Subjects (CCMO) for review.