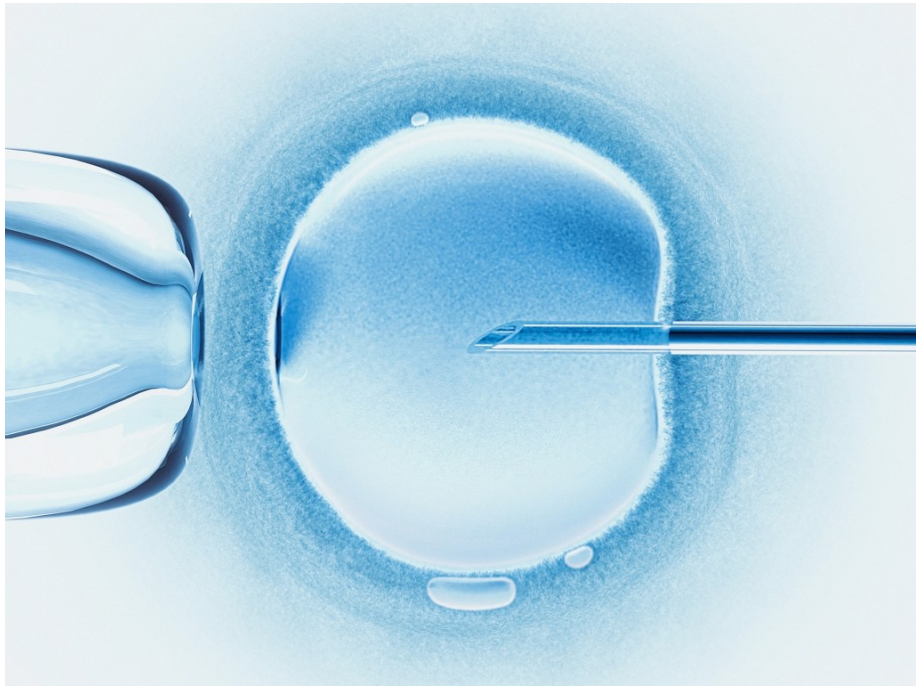
Mitochondrial Replacement Therapy

The Three-Parent-Baby



By Francisco C. and Dylan L.

13.5.2019

5A Gymnasium Kirschgarten

Table of Contents

1. Preface

When being approached by the task to choose a topic for our biology assignment concerning genetic engineering and biotechnology, we knew we wanted it to involve the human body. As we started researching genetic engineering in humans, most articles were about genetically modified babies, but this wasn't exactly what we were looking for. We stumbled upon a news article from the English newspaper "The Guardian" about a "three-parent-baby" using mitochondrial replacement therapy (MRT). It was about the first women in the UK to be allowed to undergo this procedure. The two women were carrying mitochondrial DNA (mtDNA) mutations that could cause myoclonic epilepsy.[1] This story moved us and made us want investigate the topic of mitochondrial replacement therapy.
What really caught our attention was the fact that scientists and doctors have developed a method to eradicate incurable mitochondrial diseases.

1.1 Key Questions

For our assignment, we asked ourselves the following questions:

- What research has already been conducted?
- What can we expect for the future of this therapy?
- What are the ethical aspects concerning this method?

2. Introduction

Mitochondrial replacement therapy is the process where faulty mitochondrial DNA (mtDNA) is replaced by a donor's healthy mtDNA to avoid genetic disorders such as Leigh syndrome or myoclonic epilepsy.
Mitochondria are one of the most important organelles in the human cell. They generate the main energy supply, which powers our human body.[2]

2.1 What are Mitochondrial Diseases?

Mitochondrial diseases are mostly untreatable, incurable and extremely difficult to screen for. Mitochondrial replacement therapy is therefore the only solution to prevent them. They are frequently inherited disorders that appear when the mitochondria fail to create energy.[3] There are four types of inheritance:

- Mitochondrial inheritance occurs when the mitochondria contain their own DNA and the mother then exclusively passes down the disorder. If the mitochondrial disorder is inherited in this way, there is a 100% chance of inheritance.
- Autosomal dominant inheritance: in this case each child receives a mutated copy from either parent and the chance of inheritance is 50%.
- Autosomal recessive inheritance: when the child receives one mutated copy from each parent, which generates a 25% chance of inheritance.
- In other cases, genes develop their own mutations, which are not inherited from the parents. [4]

The diseases usually occur at birth but can also be present at any age. 1'000 to 4'000 children each year are born with a mitochondrial disease. In the United States, one in 5'000 people are affected by the disorder.[4]

Fig. 1 Human muscle cells. Red fibres indicate defect mitochondria

With the use of mitochondrial replacement therapy, the persistence of these diseases can be prevented. Cytoplasmic transfer was first used in the United States in 1996. The first baby born using this procedure was in 1997.[5]

3. Engineering Technique

The engineering technique involves the transfer of a female donor's healthy mtDNA to the egg of the mother with defective mtDNA. There are two methods for the donation of mitochondrial DNA, the pronuclear transfer technique and the maternal spindle transfer technique. A third technique called cytoplasmic transfer has also been used in the past, but is now banned in the USA.[6]

3.1 Pronuclear Transfer Technique (PNT)

For this method both the mother's and the donor's egg have to be fertilized before transferring the mtDNA, therefore the eggs involved are already embryos. During the process the nucleus, containing nuclear DNA, is removed from both embryos. The mother's nucleus is then transplanted into the donor's egg, containing healthy mtDNA. Through *in vitro fertilisation* (IVF), the donor's embryo, containing the mother's nucleus, is inserted back into the mother. The quantity of donor genetic material inherited by the child lies at 0.1%.[2,7,8]

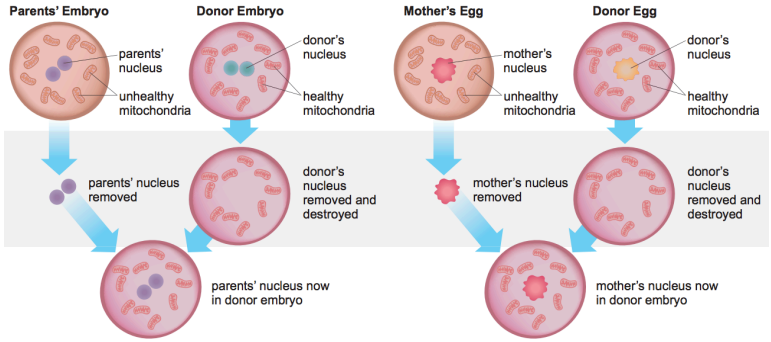


Fig. 2 Left: Summary of pronuclear transfer. Right: Summary of maternal spindle transfer

3.2 Maternal Spindle Transfer Technique (MST)

Unlike the pronuclear transfer, for the maternal spindle transfer technique, the egg is only fertilized after the nucleus transfer. But it follows the same principle, the donor's nucleus is replaced by the mother's nucleus and the donor egg is inserted into the mother. The quantity of donor genetic material inherited by the child also lies at 0.1%.[2,7,8]

3.3 Cytoplasmic Transfer Technique

This technique is completely different from the ones afore mentioned, since it does not involve transferring the nucleus from one egg to the other. For this process cytoplasm and thus mitochondria from the donor are inserted into the mother's egg, resulting in an egg with a mixture of mitochondria from both people. The process is, however, not only for avoiding mitochondrial diseases. It is also used for helping women who are infertile to have the possibility to become pregnant.[8]

The drawback concerning this method, is the quantity of genetic information of the third person in the future baby. One cannot know the possible biological effects this can have, for example the occurring of a specific condition from an ancestor of the donor. And since this procedure is quite recent, we also don't know the effects it could have on future generations. The quantity of donor genetic material inherited by the child lies slightly higher than the other procedures at 1%.[6,8]

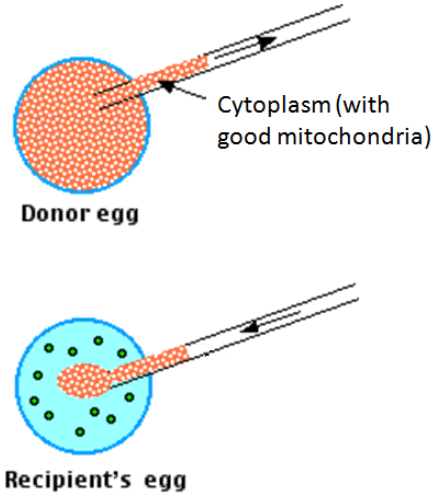


Fig. 3 Basic summary of cytoplasmic transfer

4. Interview with a Specialist

It was difficult to find an organisation which practices MRT in Basel. Therefore, we conducted a quality interview with Dr. med. Nenad Pavic-Bosshard from Fertilitas, an institution specialising in *in vitro fertilisation* situated in Basel.

Q: Do you practice the method of mitochondrial replacement therapy? What else do you practice at Fertilitas?

A: No, our main focus is *in vitro fertilisation*. We help couples who would like to have children, but are unable to conceive naturally, to achieve their dream. We offer various procedures including semen analysis, intracytoplasmic sperm injection (ICSI), which can also be done with donor sperm, and by patient's request we can also freeze egg and sperm cells for up to 5 years.

MRT concerns the eradication of diseases, while IVF is solely dedicated to child birth.

Q: Are there any important precautions for a couple wanting to undergo an IVF?

A: Yes, there are various factors which influence an IVF. The most important aspect is, in my opinion, age. It is important for women to be conscious that starting at the age of 37 they become more susceptible to infertility and more serious effects, like high possibility of the baby being born with defects. That is why we recommend the couple to make an informed choice with our help.

Another precaution would be to avoid any type of stimulants, for example smoking or consumption of alcohol. Coffee can be consumed but only in small amounts and in moderation.

Lastly, this is not really a precaution, more of a recommendation. The woman to undergo the procedure should have a healthy, balanced diet, containing enough vegetables and fruits.

Q: What, would you say, are the ethical aspects when talking about MRT and IVF?

A: I am not enough informed to make claims about MRT, but I assume the aspects are similar.

Firstly, the child is not conceived naturally, which could come as a mental burden to the parents and the child.

Secondly, IVF is not a 100% guarantee that you will become pregnant. There is an uncertainty involved, so the couple must be sure that they want to follow through.

Lastly, during IVF some embryos are destroyed, which is a great discussion in bioethics still today.

5. Discussion

When we started this project, the first question we asked ourselves was: "What research has already been conducted?" The main problem, that the therapy should combat, is the inheritance of genetic disorders originating from the mitochondrial DNA. After extensive research, scientists were able to discover a method of preventive measure. The years of research, however, were not all successful. The introduction of cytoplasmic transfer was initially seen as a beneficial process for the fertilisation of many infertile women. But it turned out to have disastrous outcomes for the child, such as the development of another disorder, which can subsequently be passed down to the future generations of its family. Since the banning of this technique in the USA (2002), more research had to be conducted, to ensure a life without developing genetic disorders.[6] Since pronuclear transfer and maternal spindle transfer were discovered, the therapy method is being more widely accepted and lately has even been applied in the UK and in Mexico.[1,9]

Our second key question is: "What can we expect for the future of this therapy?" We expect that the therapy method can only be improved to guarantee that no side effects occur. We also strongly believe that a person with three parents will be more socially accepted. Especially in this period of time where an increase of social acceptability amongst various groups can be noticed.

Our final question we posed was: "What are the ethical aspects concerning this method?" The first and most important ethical issue is the fact that a child has three parents. This opposes our classic ideology of a two-parent society. The involvement of the donor in the child's life is optional to the parents. Additionally, there is also a lot of trust invested in the donor because of his importance in the child's conceiving.

Another aspect is the fact that a mixture of genes is passed down which can lead to unknown genetic problems. This is obviously an issue because the therapy is supposed to prevent diseases, not cause them.

Finally, there is the destroying of embryos during the process. Since the embryo is already biologically considered as a person, one could say that this process "kills people".

Ultimately, there are various sides to this debate about MRT. But in our opinion the therapy technique should be allowed to be conducted. The decision of having a child and the outcome of its life lies with the parents and if this method is crucial for the survival of the child, it should be applied.

6. Summary

Summarising the paper on mitochondrial replacement therapy is fascinating and hard to acknowledge, seeing as how far the genetic engineering technique has come. With the application of MRT, scientists can now help families, affected by mitochondrial diseases, to have children while avoiding the inheritance of these devastating disorders. Although ethical issues will always persist, the method is slowly being more accepted by our society because of the benefits being discovered. Additionally, the therapy has been truly successful over the few past years in which it was applied.

The study of the engineering techniques and the outcome of the quality interview gave us a deeper understanding of not only our topic, but also of the practical appliance of *in vitro fertilisation* nowadays. We were able to use this information in order to discuss certain key questions we posed ourselves in the beginning.

To conclude, it was very interesting to research and deal with mitochondrial replacement therapy. It will be exciting to see how this process will develop in the future.

7. References

[1] https://www.theguardian.com/science/2018/feb/01/permission-given-to-create-britains-first-three-person-babies (13.5.2019)

[2] Büchler, Andrea / Parizer, Karène: Mitochondrial donation – birth of a policy. Bioethica Forum Volume 10, No. 1: 15-23. 2017

[3] Dimond, Rebecca / Stephens, Neil: Three persons, three genetic contributors, three parents: Mitochondrial donation, genetic parenting and the immutable grammar of the 'three x x'. Health Volume 22, Issue 3: 240-258. 2017

[4] https://my.clevelandclinic.org/health/diseases/15612-mitochondrial-diseases (13.5.2019)

[5] https://www.nytimes.com/2014/06/29/magazine/the-brave-new-world-of-three-parent-ivf.html?_r=0 (13.5.2019)

[6] https://www.geneticsandsociety.org/internal-content/ooplasmiccytoplasmic-transfer (13.5.2019)

[7] Feba, Jose / Lekshmi, S / Shilpa, Lal / Jiju, V / Elessy, Abraham: Three parent child: a review. IJNTPS Volume 7, No. 2: 54-56. 2017

[8] https://abaresources.co.nz/wp-content/uploads/2017/09/Genetics_Three-Parent-Babies.pdf (13.5.2019)

[9] https://www.pbs.org/newshour/science/baby-born-from-3-parents-a-victory-for-new-controversial-procedure (13.5.2019)

Title page: https://www.pbs.org/newshour/science/baby-born-from-3-parents-a-victory-for-new-controversial-procedure (13.5.2019)

Fig. 1: https://en.wikipedia.org/wiki/Mitochondrial_disease#/media/File:Ragged_red_fibres_-_gtc_-_very_high_mag.jpg (13.5.2019)

Fig. 2: https://abaresources.co.nz/wp-content/uploads/2017/09/Genetics_Three-Parent-Babies.pdf (13.5.2019)

Fig. 3: https://www.remembryo.com/oocytequality/ (13.5.2019)