

Statutory Approvals Committee – minutes

Centre 0017 (Newcastle Fertility Centre at LIFE)

Mitochondrial Donation using Pro Nuclear Transfer (PNT)

Application Reference: M0008

Mitochondrial disease OMIM #520000, #540000, caused by a mutation in *MT-TL1* (OMIM *590050)

Thursday, 26 July 2018

HFEA, 10 Spring Gardens, London, SW1A 2BU

Committee members	Margaret Gilmore (Chair) Bobbie Farsides (Deputy Chair) Anne Lampe Ruth Wilde	
Members of the Executive	Richard Chamberlain Dee Knoyle Bernice Ash Paula Robinson Catherine Burwood	Temporary Committee Clerk Committee Secretary (Observer) Committee Secretary (Observer) Head of Planning and Governance (Observer) Senior Governance Manager (Observer)
External Adviser	Professor Shamima Rahman	
Legal Adviser	Graham Miles	Blake Morgan LLP
Apologies	Anthony Rutherford	

Declarations of interest

- Members of the committee declared that they had no conflicts of interest in relation to this item.

The committee had before it:

- 8th edition of the HFEA Code of Practice
- Standard licensing and approvals pack for committee members.
- Mitochondrial Donation Explanatory Note
- Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015

The following papers were considered by the committee:

- Executive Summary
- Application Form
- Additional supportive information
- Patient letter to accompany application
- Peer review form
- Written advice of Statutory Approvals Committee's expert adviser
- PR response to written advice

1. Background

- 1.1. The Person Responsible at the Newcastle Fertility Centre submitted an application to carry out mitochondrial donation (PNT) OMIM #520000, #540000, caused by a mutation in *MT-TL1* (OMIM *590050).
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2. Consideration of application

- 2.1. The committee welcomed the clear executive summary and the advice of its Specialist Adviser Professor Shamima Rahman.
- 2.2. The committee noted that the description in the application for m.3243A>G related mitochondrial disease, OMIM #520000, #540000 caused by a mutation in the *MT-TL1* gene, OMIM *590050, is consistent with the Peer Review.
- 2.3. The committee noted that the application set out relevant information about m.3243A>G related mitochondrial disease including the medical history of the affected individual and her relevant family history.
- 2.4. The committee noted that the patient currently manifests symptoms of mitochondrial disease.

Administrative requirements

Application

- 2.5. The committee noted that the application has been submitted as required by General Direction 0008. The centre has submitted an application to perform mitochondrial donation using Pronuclear Transfer (PNT) for m.3243A>G related mitochondrial disease, OMIM #520000, #540000 caused by a mutation in the *MT-TL1* gene, OMIM *590050, for a named patient, on the relevant application form.

Licence – Express Provision and Variation

- 2.6. The committee noted that the centre's licence has an 'express provision', granted by the HFEA, to permit mitochondrial donation treatments using PNT and the centre's licence has been varied accordingly.

Embryologist

- 2.7. The committee noted that the Mitochondrial Donation Practitioner named on the centre's licence is the only embryologist licensed at the centre to perform mitochondrial donation using PNT.

Patient selection criteria

Pre-implantation Genetic Diagnosis (PGD) considered

- 2.8. The committee had regard to its Mitochondrial Donation Explanatory Note 2.5 and 7.1 (levels of heteroplasmy/homoplasmy for a particular mitochondrial DNA (mtDNA) mutation in the germ line) and reminded itself that PNT should only be offered where a patient has undergone an assessment that deems PGD inappropriate or likely to be unsuccessful.
- 2.9. The committee noted that the Peer Reviewer and the Specialist Advisor supported the centre's view that PGD would be inappropriate or likely to be unsuccessful for this patient.

Particular Risk

- 2.10. The committee had regard to its Mitochondrial Donation Explanatory Note and the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015, 8(a)(i) and considered whether there was a particular risk that any embryo which is created by the fertilisation of an egg extracted from the ovaries of a named women may have mitochondrial abnormalities caused by mtDNA.

- 2.11.** The committee noted that the application sets out information about m.3243A>G related mitochondrial disease, OMIM #520000, #540000 caused by a mutation in the *MT-TL1* gene, OMIM *590050, including the patient's family history of affected individuals, their mutation load and clinical manifestations of disease.
- 2.12.** The committee considered that the patient is at significant risk of developing further symptoms over her lifespan. The details of the particular factors underlying this rationale have been omitted to protect the identity of the patient.
- 2.13.** The committee noted the difficulty in correlating the mutational load (level of heteroplasmy) with disease severity, which is well recognised in the assessment of mitochondrial disease. The variability, and unpredictability, of the symptom complex relates to the varying mutational load in different tissues and organs, and even within the organs.

Significance and seriousness

- 2.14.** The committee had regard to its decision tree, Mitochondrial Donation Explanatory Note and the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015 8(a)(ii). The committee considered whether there is a significant risk that a person with those abnormalities will have or develop serious mitochondrial disease.
- 2.15.** The committee noted that individuals with this mutation can develop MELAS, a condition which is a progressive neuro-degenerative disorder, impacting on quality of life and long-term survival. In severe forms of the disease patients require the use of a wheel-chair, due to disabling myoclonus and ataxia, and often require assistance with all activities of daily living, including eating, washing, and dressing. Patients may also develop other symptoms including intractable seizures, encephalopathy, recurrent stroke-like episodes, diabetes, and progressive cognitive impairment. Cardiac complications include arrhythmias, cardiomyopathy and sudden death syndrome which can occur at a young age.
- 2.16.** In the later stages of MELAS, patients often require hospital admissions for management of stroke-like episodes, seizures, encephalopathy, urinary tract infections (including management of urinary obstruction), aspiration pneumonia (resulting from chronic immobility, bulbar dysfunction and gastroparesis) and bowel management that often mimics an acute surgical abdomen (resulting from chronic intestinal dysmotility). In addition, psychiatric symptoms are prominent relating to the relentlessly progressive nature of the dementing process, precipitating acute hospital admissions for management of behavioural and cognitive issues that are often resistant to conventional anti-psychosis pharmacological agents.

Mitochondrial Donation using Pronuclear Transfer (PNT)

- 2.17.** The committee noted that Mitochondrial DNA (mtDNA) mutations are collectively a relatively common cause of genetic disease. Mitochondrial donation treatment can be used for patients with a severe mitochondrial disease to reduce the risk of passing the condition onto their children. The PNT technique requires egg donation from a donor with mtDNA without defects that may cause disease. Gametes are provided by three people involved in this treatment, the mother, father and egg donor. The patient's pronucleus is removed from the egg that is known to carry a high percentage of mutated mtDNA and transferred to a healthy donor egg with its own nuclear genetic material (pronucleus) removed.

Reversion

- 2.18.** There may be some carryover of the mutant mtDNA and a theoretical risk remains of reoccurrence of significant mutant mtDNA levels in the child and subsequent generations that may lead to mitochondrial disease.

Recommendation

- 2.19.** The committee agreed to consider this application to perform mitochondrial donation using PNT for the patient named in the application.

3. Decision

Mitochondrial Donation Explanatory Note and
Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015,
8(a)(i), 8(a)(ii) and 8(b)

- 3.1.** The committee noted that authorisation for Mitochondrial Donation using Pronuclear Transfer (PNT) for mitochondrial disease OMIM #520000, #540000, *MT-TL1* gene, OMIM *590050, is conditional on the embryo subsequently being created by the fertilisation of an egg extracted from the ovaries of the women so named, Regulations 8(b).

Particular Risk

- 3.2.** On the basis of the information presented the committee was satisfied that there was a particular risk that any embryo which is created by the fertilisation of an egg extracted from the ovaries of the named woman may have mitochondrial abnormalities caused by a pathogenic mtDNA mutation.

Significant Risk

- 3.3.** On the basis of the information presented the committee was also satisfied that there was a significant risk that a person with those mitochondrial abnormalities caused by a pathogenic mtDNA mutation will have or develop serious mitochondrial disease.
- 3.4.** The committee considered the patient's family history and the manifestation of the disease along with her medical history, which shows that it is likely that any child conceived by her is likely to be at significant risk of being affected by this serious and progressive disease, which affects major organs such as the brain, heart and kidneys, severely impacting on the quality of life.

Peer review & expert advice

- 3.5.** The committee considered all of the information included in the application. The committee also considered advice from the Peer Reviewer and its Expert Adviser, Professor Shamima Rahman, on the new information provided by the centre.
- 3.6.** The committee noted the documented rationale which explained why the patient was unsuitable for pre-implantation genetic diagnosis (PGD) due to the diminished probability of obtaining eggs with sufficiently low levels of heteroplasmy (<18%) to produce a child unlikely to be symptomatically affected by mitochondrial disease, since the patient had been found to have the pathogenic m.3243A>G *MT-TL1* mutation detected at high heteroplasmy levels.

Authorised Treatment

- 3.7.** The committee agreed to authorise this application, to allow the named Mitochondrial Donation Practitioner at the centre to perform mitochondrial donation using PNT, for m.3243A>G related mitochondrial disease, OMIM #520000, #540000 caused by a mutation in the *MT-TL1* gene, OMIM *590050, for the patient named in the application. The committee recognised the right of the patient not to be identified.

HFEA Code of Practice

Counselling and support

- 3.8.** The committee encouraged the centre to ask for patients' consent to contact them following mitochondrial donation treatment, to check up on the child's health and development in the future. As this is a new technique the medical and scientific community needs to understand as much as possible about how it affects children and future generations. This will ensure they get the best possible care in the future as well as contributing to the understanding of mitochondrial disease, now and in the future, this includes patients who live abroad.
- 3.9.** The committee agreed that counselling should continue to be offered after treatment.

Welfare of the Child

- 3.10.** The committee had regard to the patient and the progressive nature of this condition, which may affect her health further in the future.
- 3.11.** The committee noted that all centres are required to have in place documented procedures to ensure that proper account is taken of the welfare of any child who may be born as a result of treatment services.

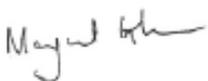
Follow up to mitochondrial donation

- 3.12.** The committee noted that, to have secured the express provision to enable the centre to undertake PNT, documented processes had to be in place at the centre, setting out how children born from mitochondrial donation will be followed up, where consent has been given. This includes long-term medical follow-up of children born as a result. The centre has close links with mitochondrial disease centres and NHS England to facilitate follow-up.
- 3.13.** The committee encouraged the centre to ask for the patient's consent to contact them following mitochondrial donation treatment and should a child be born, to check up on the child's health and development in the future. As this is a new technique, the medical and scientific community needs to understand as much as possible about how it affects children and future generations. This will ensure they get the best possible care in the future as well as contributing to the continued understanding of mitochondrial disease. The committee understands that patients do not have to agree to the follow up but should be presented with this opportunity to help others affected by mitochondrial disease, now and in the future; this includes patients who live abroad.

4. Chairs signature

I confirm this is a true and accurate record of the meeting,

Signature



Name

Margaret Gilmore

Date

24 August 2018