Statutory Approvals Committee – minutes

Centre 0017 (Newcastle Fertility Centre at LIFE)

Mitochondrial Donation using Pronuclear Transfer (PNT)

Application Reference: M0003

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	Dee Knoyle Bernice Ash Richard Chamberlain Paula Robinson Catherine Burwood	Committee Secretary Committee Secretary (Observer) Temporary Committee Clerk (Observer) Head of Planning and Governance (Observer) Senior Governance Manager (Observer)
Expert Adviser	Professor Shamima Rahman	
Legal Adviser	Graham Miles	Blake Morgan LLP
Observers		

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 update
- Application form
- Peer review form
- Executive summary
- Letter from Person Responsible - Centre 0017
- Peer Reviewer email
- Statutory Approvals Committee Expert Adviser’s written comments
- Person Responsible’s response to Statutory Approvals Committee Expert Adviser’s written comments
- 2017-11-30 Statutory Approvals Committee Minutes, Application M0003 for Mitochondrial Donation (PNT)

1. Background

1.1. The Person Responsible (PR) at Newcastle Fertility Centre at Life, centre 0017 submitted an application to carry out mitochondrial donation (PNT) for mitochondrial disease OMIM #520000, #540000, caused by a mutation in the *MT-TL1 gene,* OMIM *590050. This application was considered by the Statutory Approvals Committee at its meeting on 30 November 2017. The committee concluded that, based on the information provided, there was insufficient evidence to support the view that Pre-implantation Genetic Diagnosis (PGD) was categorically inappropriate and likely to be unsuccessful for this patient. The committee felt it could benefit from further information, should the applicant choose to re-submit the application for further deliberation, with added information addressing specific questions relating to the patient, which have been omitted from these minutes to preserve the identity of the patient.

1.2. The PR has re-submitted the application with additional information for further deliberation by the Statutory Approvals Committee at its meeting on 26 July 2018.

2. Consideration of application - reconsideration

2.1. The committee welcomed the advice of its Expert Adviser, Professor Shamima Rahman, who confirmed that the condition was as described in the papers.

2.2. The committee noted that the description in the application for 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 had regard to its decision tree.

Administrative requirements

Application

2.4. 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 mitochondrial disease OMIM #520000, #540000, caused by a mutation in *MT-TL1 gene,* OMIM *590050, for a named patient, on the relevant application form.

Licence - Express Provision and Variation

2.5. 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

2.6. 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

2.7. 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.

2.8. The committee noted that the Peer Reviewer originally supported the centre's view that PGD would be inappropriate or likely to be unsuccessful for this patient and continues to support that view with the additional information provided.

2.9. The committee discussed the new information provided by the applicant. The committee noted that the Expert Adviser to the committee, Professor Shamima Rahman, was satisfied with the centre's response to the committee's private questions relating to the patient, including the centre's conclusion that PGD would be inappropriate or likely to be unsuccessful. The additional information submitted suggested that the probability that this patient would have eggs with a level of heteroplasmy low enough to produce a child unlikely to be symptomatically affected by mitochondrial disease was low and therefore PGD would not be a suitable reproductive choice 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 mitochondrial disease OMIM #520000, #540000, caused by a mutation in *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 mutant 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 mutant load in different tissues and organs, and even within the organs.

Significance & 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 the onset of mitochondrial disease OMIM #520000, #540000, caused by a high load of mutation in the *MT-TL1* gene, OMIM *590050, could be as early as the first few months of life presenting as Leigh syndrome, a severe neurological disorder.

2.16. Individuals can develop MELAS, Mitochondrial Encephalopathy, Lactic acidosis, OMIM #540000, resulting in stoke-like episodes and seizures, with all the secondary complications of impaired movement and declining cerebral functions.

2.17. Individuals can also develop MIDD, Maternally Inherited Diabetes & Deafness, OMIM #520000 resulting in diabetes, visual and hearing impairment.

2.18. Other symptoms of the disease included sudden death due to cardiac arrest and some individuals live with an unawareness of this vulnerability. The kidney function can also deteriorate, requiring a kidney transplant. In the worst-case scenario, multi-organ/multi-system tissues are affected.

2.19. There are few effective treatments for the disease and there is no known cure. Due to the multi-organ/multi-system nature of this disease, organ-specific strategies are often implemented, including conventional anti-seizure drugs for epilepsy and the management of diabetes, standard pharmacologic therapy for cardiac and renal involvement, physiotherapy to improve impaired motor function and the provision of hearing aids and visual aids.

Mitochondrial Donation using Pronuclear Transfer (PNT)

2.20. 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

2.21. 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

2.22. The committee agreed to reconsider this application to perform mitochondrial donation using PNT for the patient named in the application, with the additional information provided.

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, caused by a mutation in the *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 multi-organ/multi-system and progressive disease which severely impacts the quality of life.

Peer Review & Expert Advice

3.5. The committee considered all of the information, including additional information provided by the centre since the first application was submitted. The committee also considered advice from the Peer Reviewer and its Expert Adviser, Professor Shamima Rahman, on the new information provided by the centre.

Authorised Treatment

3.6. The committee agreed to authorise this application, to allow Dr Louise Hyslop, Mitochondrial Donation Practitioner at the centre to perform mitochondrial donation using PNT, for 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

3.7. The committee agreed that the centre should follow procedures in accordance with the HFEA Code of Practice and pay particular attention to the areas highlighted below in relation to mitochondrial donation:

Counselling and support

3.8. The committee emphasised that the centre needs to fulfil the HFEA's counselling requirements for all involved in mitochondrial donation and provide the necessary patient information. The committee noted that this would include consideration of the risks involved to enable patients to make fully informed choices.

3.9. The committee agreed that counselling should continue to be offered after treatment.

Welfare of a 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

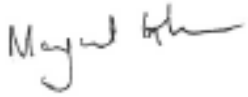
3.12. The committee noted that, to have secured the express provision to enable the centre to undertake PNT, documented processes had to be in place at the centre, setting out how children born from mitochondrial donation will be followed up, where consent has been given. This includes long-term medical 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. Chair's signature

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

Signature



Name

Margaret Gilmore

Date

24 August 2018