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, 30 November 2017

HFEA, 10 Spring Gardens, London, SW1A 2BU

Committee members	Margaret Gilmore (Chair) Anne Lampe Tony Rutherford Bobbie Farsides	
Members of the Executive	Dee Knoyle	Committee Secretary
External adviser	Professor Shamima Rahman	
Legal Adviser	Philip Grey	Mills & Reeve 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 Summary
- Mitochondrial Donation: new case application form
- Peer Review Form

1. Consideration of application

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

1.2. The committee noted that the description in the application for mitochondrial disease OMIM #520000, #540000, caused by a mutation in MT-TL1 (OMIM #590050) is consistent with the Peer Review.

1.3. The committee had regard to its decision tree.

Administrative requirements

Application

1.4. 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 (OMIM #590050) for a named patient, on the relevant application form.

Licence - Express Provision and Variation

1.5. 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

1.6. 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

1.7. 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.

1.8. The Committee noted that the Peer Reviewer supported the centre's view that PGD would be inappropriate and likely to be unsuccessful for this patient. However, the Committee raised a number of questions when considering this alongside the patient's particular circumstances and in discussion with the Specialist Adviser. Details of this discussion have been omitted to protect the identity of the patient.

1.9. The committee highlighted that PGD is performed at the 'blastocyst' stage and therefore a number of cells could be used for analysis. The Specialist Adviser also informed the committee of two publications from the group of Professor Hubert Smeets in Maastricht, the Netherlands:

> Hellebrekers DM, Wolfe R, Hendrickx AT, de Coo IF, de Die CE, Geraedts JP, Chinnery PF, Smeets HJ. PGD and heteroplasmic mitochondrial DNA point mutations: a systematic review estimating the chance of healthy offspring. Hum Reprod Update. 2012 Jul;18(4):341-9. doi: 10.1093/humupd/dms008. Epub 2012 Mar 28. Review. PubMed PMID: 22456975.and
>
> Sallevelt SCEH, Dreesen JCFM, Coonen E, Paulussen ADC, Hellebrekers DMEI, de Die-Smulders CEM, Smeets HJM, Lindsey P. Preimplantation genetic diagnosis for mitochondrial DNA mutations: analysis of one blastomere suffices. J Med Genet. 2017 Oct;54(10):693-697. doi: 10.1136/jmedgenet-2017-104633. Epub 2017 Jul 1. PubMed PMID: 28668821.

1.10. Hellebrekers et al 2012 stated that 'carriers of heteroplasmic mtDNA mutations will have a fair chance of having healthy offspring, by applying PGD', whilst Sallevelt et al 2017 asserted that analysis of one blastomere suffices for PGD for mtDNA mutations.

Particular Risk

1.11. 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.

1.12. The committee noted that the application sets out information about mitochondrial disease OMIM #520000, #540000, caused by a mutation in MT-TL1 (OMIM #590050), including the patient's family history of affected individuals, their mutation load and clinical manifestations of disease.

1.13. 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.

1.14. 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

1.15. 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.

1.16. The committee noted that the onset of mitochondrial disease OMIM #520000, #540000, caused by a mutation in MT-TL1 (OMIM #590050) could be as early as the first few months of life starting with Leigh Syndrome, a severe neurological disorder.

1.17. 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.

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

1.19. 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.

1.20. 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.

Recommendation

1.21. The committee noted the inspectorate's recommendation to consider this application to perform mitochondrial donation using PNT for the patient named in the application.

2. Decision

2.1. The committee noted that authorisation for Mitochondrial Donation using Pronuclear Transfer (PNT) for mitochondrial disease OMIM #520000, #540000, caused by a mutation in MT-TL1 (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).

2.2. The committee considered the information submitted by the inspectorate which included the centre's application form and the Peer Review. The committee also considered the advice provided by its Specialist Adviser.

2.3. The committee concluded that, based on the information provided, there was insufficient evidence to support the view categorically that PGD was 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 its 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. The Committee has asked that these specific questions be sent confidentially to the Applicant.

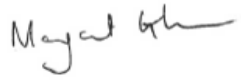
2.4. The committee also requested confirmation from the centre on whether to include the gene OMIM #590050.

2.5. The committee recognised the right of the patient not to be identified.

3. Chair's signature

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

Signature



Name

Margaret Gilmore

Date

25 January 2018