Statutory Approvals Committee – minutes

Centre 0017 (Newcastle Fertility Centre at LIFE)

Mitochondrial Donation using Pronuclear Transfer (PNT)

Application Reference: M0004

MERRF Syndrome (Myoclonic Epilepsy with Ragged Red Fibres), OMIM #545000, caused by a mutation in the MTTK gene, OMIM *590060

Thursday, 30 August 2018

HFEA, 10 Spring Gardens, London, SW1A 2BU

Committee members	Margaret Gilmore (Chair) Bobbie Farsides (Deputy Chair) Anne Lampe Ruth Wilde Anthony Rutherford	
Members of the Executive	Catherine Burwood Bernice Ash Paula Robinson Stevan Cirkovic	Committee Secretary Committee Secretary (Observer) Head of Planning and Governance (Observer) Policy Officer (Observer)
Expert Adviser	Professor Peter Braude	
Legal Adviser	Jane Williams	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:

- Reapplication Executive Summary

Part 1 (previous application)

- Executive Summary
- Application form
- Clinical expert review form
- 2018-01-25 SAC Minutes, Application M0004, to offer PNT to a specified patient

Part 2

- Letter from PR - reapplication of M0004
- Response to letter, from peer reviewer
- SAC expert adviser's written advice
- SAC expert adviser's presentation
- PR's response to SAC adviser's written comments

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 MERRF syndrome (Myoclonic Epilepsy with Ragged Red Fibres), OMIM #545000, caused by a mutation in the MTTK gene, OMIM *590060. This application was considered by the Statutory Approvals Committee at its meeting on 25 January 2018. The committee concluded that it would adjourn its decision to authorise mitochondrial donation using PNT for the patient named in the application until a comprehensive analysis of the published data was provided in a way that made it explicit that further cycles of pre-implantation genetic diagnosis (PGD) would be unhelpful in this case. In the course of its discussion, the committee also commented that it may have been beneficial to have further information about the risk of a child developing MERRF syndrome in a severe form, in this case.

1.2. The PR re-submitted the application with additional information for further deliberation by the Statutory Approvals Committee at its meeting on 30 August 2018.

2. Consideration of application - reconsideration

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

2.2. The committee noted that the description in the application for MERRF syndrome (Myoclonic Epilepsy with Ragged Red Fibres), OMIM #545000, caused by a mutation in the MTTK gene, OMIM *590060, 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 had been submitted as required by General Direction 0008. The centre has submitted an application to perform mitochondrial donation using Pronuclear Transfer (PNT) for MERRF syndrome, OMIM #545000, 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, details of which have been omitted to protect the patient's identity. The committee noted that the Expert Adviser to the committee, Professor Peter Braude, advised that PGD was more likely to be unsuccessful than it was to be successful for this patient, her previous PGD history providing further information about mutation load and embryo quality. He advised that PGD would not be a suitable reproductive choice for the 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, Regulation 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 MERRF syndrome, including the patient's clinical history and family history of affected individuals, their mutation load and clinical manifestations of the disease.

2.12. The committee considered that the patient is at risk of developing symptoms over her lifespan and has a clearly identified pathogenic mutation. 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 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, Regulation 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 clinical features of this condition are often devastating. Symptoms are predominantly neurological and include myoclonus (sudden, involuntary jerking of a muscle or group of muscles), epilepsy, myopathy, ataxia (the loss of full control of bodily movements) and cognitive impairment. However, MERRF syndrome is a multi-system disease with frequent cardiac involvement and metabolic disturbances. The ragged red fibres in the original description refer to the appearance on the muscle biopsy and represent mitochondrial proliferation as a response to the respiratory chain deficiency, an underlying hallmark of the disease. Clinical features are often highly variable between individuals and between family members. It is frequently a progressive disorder, with few effective treatments and no known cures for those clinically affected, resulting in high disability and premature death. The disease can also cause significant motor and intellectual disability.

2.16. MERRF syndrome impacts considerably on the quality of life and long-term survival. In severe forms of the disease, patients require the use of a wheelchair, 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 visual loss due to optic nerve involvement, intractable seizures, cognitive impairment, bulbar dysfunction, cardiac arrhythmias and cardiomyopathy. In the later stages of disease progression, patients often require regular hospital admissions for treatment of complications of the disorder including urinary tract infections and aspiration pneumonia with end-stage disease often relating to cardiorespiratory failure, necessitating ventilator support.

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.

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 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,

Regulations 8(a)(i), 8(a)(ii) and 8(b)

3.1. The committee noted that authorisation for Mitochondrial Donation using Pronuclear Transfer (PNT) for MERRF syndrome, OMIM #545000, caused by a mutation in the MTTK gene, OMIM *590060, is conditional on the embryo subsequently being created by the fertilisation of an egg extracted from the ovaries of the women so named, Regulation 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 indicates 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.

Authorised Treatment

3.6. The committee agreed to authorise this application, to allow the Mitochondrial Donation Practitioner named on the centre's licence to perform mitochondrial donation using PNT, for MERRF syndrome OMIM #545000, caused by a mutation in the MTTK gene, OMIM *590060, 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 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

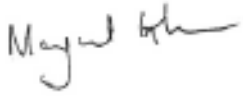
3.11. The committee noted that, to have secured the express provision to enable the centre to undertake PNT, documented processes had to be in place at the centre, setting out how children born from mitochondrial donation will be followed up, where consent has been given. This includes long-term medical follow-up of children born as a result. The centre has close links with mitochondrial disease centres and NHS England to facilitate follow-up.

3.12. 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

28 September 2018