Statutory Approvals Committee – minutes

Centre 0017 (Newcastle Fertility Centre at LIFE)

Mitochondrial Donation using Pronuclear Transfer (PNT)

Application Reference: M0001

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

Thursday, 31 August 2017

HFEA, 10 Spring Gardens, London, SW1A 2BU

Committee members	Margaret Gilmore (Chair) Anne Lampe Tony Rutherford Ruth Wilde Bobbie Farsides	
Members of the Executive	Dee Knoyle	Committee Secretary
External adviser	Prof Shamima Rahman	
Legal Adviser	Sarah Ellson	Fieldfisher 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
- Clinical Expert Review Form

1. Consideration of application

1.1. The committee welcomed the advice of its Specialist Adviser, Prof Shamima Rahman, who confirmed that the condition was as described in the papers. She further confirmed that the evidence submitted by the clinic supported the view that PGD was inappropriate or likely to be unsuccessful.

1.2. The committee noted the description in the application for MERRF Syndrome (Myoclonic Epilepsy with Ragged Red Fibres), OMIM #545000, caused by a mutation in the MTTK gene (the details of which have been omitted to protect the identity of the patient).

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 MERRF Syndrome, OMIM #545000 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 procedure would be carried out by the embryologist named on the centre's licence, who 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 application includes a documented rationale as to why PGD may be deemed inappropriate and likely to be unsuccessful in this case. The details of the particular factors underlying this rationale have been omitted to protect the identity of the patient.

1.9. The application has been reviewed by a clinical expert who confirmed the condition was as outlined in the application, and expressed the view that the evidence provided does not support the use of PGD in this case.

Particular risk

1.10. 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.

1.11. The committee noted the evidence that the patient has a clearly identified pathogenic mutation which gives rise to a considerable risk of any children having serious mitochondrial disease.

1.12. The committee noted that the application sets out relevant information about MERRF syndrome including the patient's family history of affected individuals, their mutation load and clinical manifestations of disease.

Significance and seriousness

1.13. 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.

1.14. The committee was satisfied on the evidence before it that the patient and her offspring are at risk of developing symptoms over their life spans.

1.15. The committee noted that where the mutation is heteroplasmic, the proportion of affected mtDNA versus unaffected mtDNA (known as the mutant mtDNA load) often correlates with the symptoms, with higher loads associated with more severe symptoms. However this is not always the case and a review of the literature does not permit the estimation of an accurate threshold to determine phenotypic expression.

1.16. The committee noted that MERRF syndrome can be, in its worst case scenario, a devastating, progressive, neurodegenerative disorder, impacting considerably on quality of life and long-term survival. MERRF syndrome is characterised by progressive myoclonic epilepsy, ataxia and weakness. Other common findings include pigmentary retinopathy, optic atrophy, deafness, lactic acidosis, lipomata, cognitive impairment and cardiac conduction defects. Due to the multi-systemic and progressive nature of MERRF syndrome, this condition can result in high morbidity and early death, often from cardio-respiratory failure before the sixth decade of life, and frequently death occurs much earlier than this.

Recommendation

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

Additional observations

1.18. The committee noted that MERRF Syndrome has already been approved for PGD by the HFEA and is listed on the PGD Approved List on the HFEA website.

Reversion

1.19. 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. 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.

1.20. The committee noted that the patient and her partner had shown an awareness of this in their statement.

Follow up to mitochondrial donation

1.21. 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.

Welfare of a child

1.22. 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.

2. Decision

2.1. 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).

2.2. The committee had regard to its Mitochondrial Donation Explanatory Note and the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015, 8(a)(i), 8(a)(ii) and 8(b). 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 may be affected with this serious multi-systemic and progressive disease which severely impacts on affected individuals' quality of life, often resulting in high morbidity and early death.

2.3. 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 and a significant risk that a person with those abnormalities will have or develop serious mitochondrial disease.

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

Follow up to mitochondrial donation

2.5. 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 understand 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.

Counselling and support

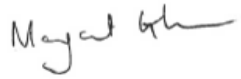
2.6. The committee wished to emphasise that the centre needs to fulfil the HFEA's counselling requirements for all involved in mitochondrial donation and provide the necessary patient information.

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

3. Chair's signature

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

Signature



Name

Margaret Gilmore

Date

18 September 2017