Statutory Approvals Committee – minutes

Item 1

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, 25 January 2018

Church House Westminster, Dean's Yard, Westminster SW1P 3NZ

Committee members	Margaret Gilmore (Chair) Anne Lampe Tony Rutherford Ruth Wilde	
Members of the Executive	Dee Knoyle Bernice Ash Nana Gyamfi Chereena Harriott	Committee Secretary Committee Secretary (Observing) Licensing Information Officer (Observing) Inspections & Logistics Officer (Observing)
External Expert Adviser	Professor Patrick Chinnery	
Legal Adviser	Dawn Brathwaite	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 Expert Adviser, Professor Patrick Chinnery, who confirmed that the condition was as described in the papers; however he pointed out that the age of onset for this condition is more generally between 25 to 35 years, as opposed to childhood.

1.2. 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 (the details of which have been omitted to protect the identity of the patient) 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 MERRF Syndrome, OMIM #545000, caused by a mutation in the MTTK gene, OMIM *590060 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 centre has a Mitochondrial Donation Practitioner named on the centre's licence. This 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.

Application

1.8. 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.

Peer Reviewer

1.9. The Peer Reviewer is supportive of this application and described the inappropriateness of the use of PGD for this patient.

Expert Adviser

1.10. The Expert Adviser reviewed the application and stated that the documented rationale used to assess whether PGD would be inappropriate or likely to be unsuccessful was not clear based on the evidence presented in the application. He cited a publication (Brain 1998;121:1889-1994) where the risk of clinical recurrence for women harbouring <80% heteroplasmy blood was <20%, and none of the 22 offspring born to mothers with <40% heteroplasmy in blood were affected. Thus, based on published data, the clinical recurrence risk for this patient was low, based on the level of heteroplasmy measured in the patient's blood. The Expert Adviser also noted that a range of heteroplasmy values was measured in the disaggregated embryos from the patient, which were, in at least one instance, substantially lower than the level measured in the patient's tissues. This raises the possibility that the patient could have a child with a significantly lower mutation load. The Expert Advisor noted the recent publications cited in the application which described case series of patients with the same mutation; however, the information in these publications was not presented in a way that showed that PGD would be inappropriate or unsuccessful in this case. The Expert Adviser suggested that a comprehensive analysis of the published data might substantiate the claims made in the application, but that this was not explicitly demonstrated in the application.

1.11. The Expert Adviser was of the view that in the absence of an analysis of the statistical data he was unable to advise on whether PGD would be inappropriate or likely to be unsuccessful in this case.

The Statutory Approvals Committee

The committee noted that review of the published literature does not permit the estimation of an accurate threshold to determine phenotypic expression in mitochondrial disease caused by this particular mutation of the MTTK gene.

Particular risk

1.12. 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.

1.13. The committee noted the evidence that the patient has a clearly identified pathogenic mutation.

1.14. The committee noted that the application sets out relevant information about MERRF Syndrome, OMIM #545000, caused by a mutation in the MTTK gene, OMIM *590060, including the patient's family history of affected individuals, their mutation load and clinical manifestations of disease.

Significance and seriousness

1.15. The committee had regard to its 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 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 hall mark 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.

1.17. 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 arrythmias 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.

Recommendation

1.18. 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

1.19. 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.

2. Decision

2.1. 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).

2.2. The committee noted that authorisation for Mitochondrial Donation using Pronuclear Transfer (PNT) for MERRF, 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).

2.3. The committee considered this application in great depth. The committee reviewed the application form, the patient's family history and manifestation of the disease along with her medical history. The committee also noted the Peer Reviewer's comments.

2.4. The committee noted the reference in the application to the position that where the mutation is heteroplasmic, there is no correlation between the proportion of affected mtDNA versus unaffected mtDNA (known as the mutant mtDNA load) and symptoms or no statistical differences in the mutant DNS heteroplasmy levels between asymptomatic carriers and clinically affected individuals.

2.5. The committee considered the advice provided by its Expert Adviser and decided to adjourn its decision to authorise mitochondrial donation using PNT for the patient named in this application until a comprehensive analysis of the published data is provided in a way that makes it explicit that further cycles of PGD would be unhelpful in this case.

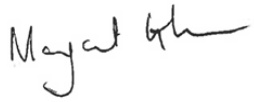
2.6. In the course of its discussion, the committee also commented that it may have been beneficial to have further information (if available) about the risk of a child developing MERRF syndrome in a severe form, in this case.

2.7. 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

13 March 2018