Statutory Approvals Committee – minutes

Centre 0017 (Newcastle Fertility Centre at LIFE)

Mitochondrial Donation using Pronuclear Transfer (PNT)

Application Reference: M0005

m.3243A>G related mitochondrial disease, OMIM #540000, #520000

Thursday, 25 January 2018

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

Committee members	Margaret Gilmore (Chair) Anne Lampe Anthony Rutherford Ruth Wilde	
Members of the Executive	Bernice Ash Dee Knoyle Nana Gyamfi Chereena Harriott	Committee Secretary Committee Secretary (Observing) Licensing Information Officer (Observing) Inspections & Logistics Officer (Observing)
Expert adviser	Prof 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
- Clinical Expert Review Form

1. Consideration of application

1.1. The committee welcomed the advice of its Expert Adviser, Prof Patrick Chinnery, who confirmed that the condition was as described in the papers.

1.2. The committee noted the description in the application for m.3243A>G related mitochondrial disease, OMIM #540000, #520000, caused by m.3243A>G tRNA Leu (UUR); MTTL1 gene mutation (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 for m.3243A>G related mitochondrial disease, OMIM #540000, #520000, caused by m.3243A>G tRNA Leu (UUR); MTTL1 gene mutation, 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 and the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015, 8(a)(ii). (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 from these minutes to protect the identity of the patient.

1.9. The committee noted that the Peer Reviewer supported the centre's view that PGD would be inappropriate or unlikely to be successful for this patient. However, the Expert Adviser, in discussion with the committee, raised some questions when considering this alongside the patient's particular circumstances. Details of this discussion have been omitted to protect the identity of the patient.

1.10. The committee noted that the application referenced Mitochondrial Encephalomyopathy, Lactic acidosis syndrome (MELAS), a progressive, neurogenerative disease, associated with this genetic mutation. The Expert Adviser referred to the committee to a publication entitled:

Victoria Nesbitt, Robert D S Pitceathly, Doug M Turnbull, Robert W Taylor, Mary G Sweeney,3 Ese E Mudanohwo, Shamima Rahman, Michael G Hanna, Robert McFarland. The UK MRC Mitochondrial Disease Patient Cohort Study: clinical phenotypes associated with the m. 3243A>G mutation—implications for diagnosis and management. J Neurol Neurosurg Psychiatry 2013- 84: 936-938 originally published online January 25, 2013.

1.11. The committee noted that the 69 patients involved in this study were considered to have a mitochondrial phenotype that should prompt screening for m.3243A>G mutation. Results of this study concluded that only 10% of patients with the m.3243A>G exhibited classical symptoms of MELAS syndrome. Other patients had a milder phenotype.

1.12. The Expert Adviser informed the committee that some centres in Europe, including in Maastricht, the Netherlands, offer PGD for patients with the m.3243A>G mutation. Embryos with <15% heteroplasmy are considered to be at low risk of recurrence in that centre, and are implanted following PGD.

Particular risk

1.13. 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.

1.14. The committee noted that the application sets out relevant information about m.3243A>G-related mitochondrial disease, OMIM #540000, #520000, caused by m.3243A>G tRNA Leu (UUR); MTTL1 gene mutation, 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 stroke or stroke-like events and seizures resistant to conventional treatments affect a small proportion of patients with mitochondrial disease, but the incidence is higher in those that harbour a particular genetic mutation, m.3243A >G, in mitochondrial DNA. However, based on the publication cited in para 1.10, only 10% of affected individuals develop the MELAS syndrome.

1.17. Individuals with this mutation can also suffer from deafness, poor vision, diabetes, muscle weakness, poor gut motility which may progress to gut failure, enlarged hearts that may progress to heart failure, and deteriorating kidney function, that may necessitate kidney transplant. There have also been reports of an increased association with people who harbour this genetic mutation suffering death at a young age, who were otherwise thought to be healthy.

1.18. The committee noted that individuals can develop MELAS, Mitochondrial Encephalopathy, Lactic acidosis, OMIM #540000, resulting in stroke like episodes and seizures. It is often a devastating, progressive, neurodegenerative disorder, impacting considerably on quality of life and long-term survival. In severe forms of the disease, patients require the use of a wheel-chair, due to disabling myoclonus (sudden, involuntary jerking of a muscle or group of muscles) and ataxia (the loss of full control of bodily movements), and often require assistance with all activities of daily living, including eating washing and dressing. Patients may also develop other symptoms including intractable seizures, encephalopathy, recurrent stroke-like episodes, progressive cognitive impairment resulting in dementia, diabetes, deafness, neuropathy, gastro-intestinal dysmotility (including Intestinal pseudo-obstruction) and cardiac complications (including arrhythmias, cardiomyopathy and sudden death syndrome).

1.19. In the later stages of MELAS, patients often require hospital admissions for management of stroke-like episodes, seizures, encephalopathy, urinary tract infections (including management of urinary obstruction), aspiration pneumonia (resulting from chronic immobility, bulbar dysfunction and gastroparesis) and bowel management that often mimics an acute surgical abdomen (resulting from chronic intestinal dysmotility). In addition, psychiatric symptoms are prominent cogent to the relentlessly progressive nature of the dementing process, precipitating acute hospital admissions for management of behavioural and cognitive issues that are often resistant to conventional anti-psychosis pharmacological agents.

1.20. The committee noted the advice from the Expert Adviser that this particular mutation can exist in 1 in 300 healthy individuals in the United Kingdom, without any symptoms at all. Patients with this m.3243A >G-related mitochondrial disease are likely to have a disability such as diabetes and deafness, but are unlikely to develop MELAS.

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 m.3243A>G-related mitochondrial disease, OMIM #540000, #520000, caused by m.3243A>G MTTL1 gene mutation, 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 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 the Expert Adviser.

2.3. The committee had regard to its Decision Tree, Mitochondrial Donation Explanatory Note and the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015, 8(a)(i), 8(a)(ii) and 8(b).

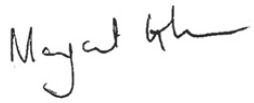
2.4. The committee concluded that, based on the information provided, specifically referencing that supplied by the Expert Adviser, concerning the undertaking of PGD, in centres within Europe, for patients with the m.3243A>G mutation, there was insufficient evidence to support the view that PGD was inappropriate or unlikely to be successful for this patient.

2.5. The committee therefore accordingly refused to authorise the application for m.3243A>G related mitochondrial disease, OMIM #540000, #520000, caused by m.3243A>G tRNA Leu (UUR); MTTL1 gene mutation. It is open to the clinic to reapply with additional information, should it choose to do so.

3. Chair's signature

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

Signature



Name

Margaret Gilmore

Date

9 February 2018