Statutory Approvals Committee – minutes

Centre 0017 (Newcastle Fertility Centre at LIFE)

Mitochondrial Donation using Pronuclear Transfer (PNT) Application Reference: M0016 to avoid MERRF (Myoclonic Epilepsy and Ragged Red Fibres), OMIM #545000, caused by a mutation in the MT-TK gene

Thursday, 26 September 2019

HFEA, Spey Meeting Room, Level 2, 10 Spring Gardens, London, SW1A 2BU

Committee members	Margaret Gilmore (Chair) Anne Lampe Emma Cave Ruth Wilde	
Members of the Executive	Moya Berry Catherine Burwood	Committee Licensing Manager
Expert Adviser	Professor Julie Steffann	
Legal Adviser	Tom Rider	FieldFisher LLP
Observers	Bernice Ash	Committee Officer

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:

- 9th 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
- Application Form
- Peer Review Form
- Written advice of the Statutory Approvals Committee Adviser
- Person Responsible response to written advice

1. Consideration of application

1.1. The committee welcomed the advice of its expert adviser, Professor Julie Steffann, who confirmed that the condition was as described in the papers.

1.2. The committee noted that the description in the application to perform mitochondrial donation using PNT in a specified patient, to avoid the inheritance of MERRF (Myoclonic Epilepsy with Ragged Red Fibres) OMIM # 545000 caused by m.8344A>G in the MT-TK gene, OMIM *590060, which encodes the mitochondrial transfer RNA for lysine, is consistent with the peer review.

Administrative requirements

Application

1.3. The committee noted that an 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 (Myoclonic Epilepsy with Ragged Red Fibres) caused by m.8344A>G in the MT-TK gene, for a named patient, on the relevant application form.

Licence - Express Provision and Variation

1.4. 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

1.5. 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

1.6. 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 took account of the fact that PNT should only be offered where a patient has undergone an assessment that deems PGD inappropriate or likely to be unsuccessful.

Peer Review Advice

1.7. The committee noted that the application has been reviewed by the peer reviewer. The peer reviewer's assessment is supportive of the application, describing the inappropriateness of PGD in this case.

Expert Advice

1.8. The committee noted the advice of the expert adviser who confirmed the patient is heteroplasmic for the m.8344A>G mutation at high mutant levels (>80% in all the patient's tested tissue) and is expected to transmit high mutant loads to her progeny. The expert adviser was also of the view that PGD was unlikely to be successful.

Particular Risk

1.9. 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 the patient may have mitochondrial abnormalities caused by mtDNA.

1.10. The committee noted that the application sets out information about MERRF, caused by a mutation in the MT-TK gene (m.8344A>G), and includes the patient's clinical history and family history of affected individuals, the mutation load and clinical manifestations of the disease.

1.11. The application describes that the patient is heteroplasmic for the MT-TK mutation which can cause MERRF. The m.8344A>G MT-TK mutation has been detected at 88% heteroplasmy in urine derived DNA, 82% in blood derived DNA and 86% in buccal epithelia derived DNA in this patient's samples. Within this pedigree, family members manifest with serious mitochondrial disease at heteroplasmy levels lower than that detected in this patient.

1.12. This committee noted that the patient is clinically affected by a serious form of mitochondrial disease with multi-organ involvement.

1.13. The committee considered that the patient has a clearly identified pathogenic mutation. The details of the factors underlying this rationale have been omitted to protect the identity of the patient.

Significance and Seriousness

1.14. The application sets out relevant information about MERRF including the family history of affected individuals, their mutation load and clinical manifestations of the disease.

1.15. The committee noted that patients harbouring the m.8344A>G mutation have been identified in many cohorts and their clinical features 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 multisystem disease with frequent cardiac involvement and metabolic disturbances. The ragged red fibres 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. After normal early development, onset is usually in childhood with clinical features often highly variable between individuals and between family members. Unfortunately, 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.

1.16. MERRF may impact considerably on quality of life and long-term survival for these patients. 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 and cardiac arrhythmias +/- 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.

Peer Reviewer & Expert Advice

1.17. The expert adviser was supportive of the application for Pronuclear Transfer (PNT) for MERRF, caused by a mutation in the MT-TK gene (m.8344A>G). The peer reviewer was also supportive of the application and considered enough information was available to make an assessment on the significant risk and stated that high mutation loads above 85% often correlate with severe disease. Mothers with high mutation loads above 70% are more likely to have children with higher loads of 85-90% and therefore have a higher chance of having severely affected offspring.

Legal Advice

1.18. The legal adviser referred the committee to relevant parts of the Mitochondrial Donation Explanatory Note and reminded the committee of its obligations to consider the patient's family history of affected individuals, their mutation load (if it may be relevant), age of onset and clinical manifestations of the disease. The committee was advised that this application was to be considered on a case by case basis taking these particulars into account and considering the worst-case scenario for this particular patient and her offspring.

1.19. 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.

Mitochondrial Donation using Pronuclear Transfer (PNT)

1.20. The committee noted that Mitochondrial DNA (mtDNA) mutations are collectively a relatively common cause of genetic disease. Mitochondrial donation can be used as treatment for patients with a severe mitochondrial disease in order to reduce the risk of passing this maternally inherited condition on to 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

1.21. 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

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

2. Decision

Mitochondrial Donation Explanatory Note and

Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015,

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

2.1. The committee noted that authorisation for Mitochondrial Donation using Pronuclear Transfer (PNT) for MERRF, caused by a mutation in the MT-TK gene (m.8344 G>A), 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).

Pre-implantation Genetic Diagnosis (PGD) - Patient selection criteria

2.2. The committee considered the advice presented in the updated application as well as the advice from the peer reviewer and the expert adviser and agreed that PGD would not be suitable in this case.

Particular Risk

2.3. Based on 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 patient may have mitochondrial abnormalities caused by a pathogenic mtDNA mutation.

Significant Risk

2.4. Based on 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.

2.5. 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 disease which could severely impact on the quality of life.

Peer Review & Expert Advice

2.6. The committee considered the information provided by the centre. The committee also considered advice from the peer reviewer and the expert adviser to the committee.

Authorised Treatment

2.7. 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, caused by a mutation in the MT-TK gene (m.8344A>G) for the patient named in the application. The committee recognised the right of the patient not to be identified.

HFEA Code of Practice

2.8. 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

2.9. 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.

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

Welfare of a child

2.11. 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.

2.12. The committee acknowledged that the centre is responsible for providing the patient with relevant information concerning her treatment to make fully informed ongoing decisions which may affect her health in the future

2.13. Considering the serious and frequently progressive nature of this condition, the committee expressed its concern for the health and welfare of the applicant and any child born. Therefore, the committee clearly states the expectation that the clinic will undertake due diligence to assess the health and welfare of both the applicant and the child during and after treatment.

Follow up to mitochondrial donation

2.14. 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

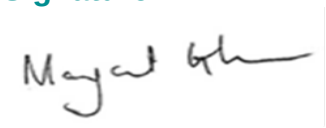
includes long-term medical follow-up of children born as a result. The centre has close links with mitochondrial disease centres and NHS England to facilitate follow-up.

2.15. 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.

3. Chairs signature

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

Signature



Name
Margaret Gilmore

Date
28 October 2019