Statutory Approvals Committee – minutes

Centre 0017 (Newcastle Fertility Centre at LIFE)
Mitochondrial Donation using Pronuclear Transfer (PNT)
Application Reference: M0014
Leber Hereditary Optic Neuropathy (LHON), caused by a mutation in the MT-ND4 gene (m.11778 G>A)

Thursday, 31 January 2019

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

Committee members	Margaret Gilmore (Chair) Bobbie Farsides (Deputy Chair) Anne Lampe Ruth Wilde Rachel Cutting Emma Cave	
Members of the Executive	Dee Knoyle Bernice Ash Paula Robinson Sandrine Oakes Nicola Lawrence	Committee Secretary Committee Secretary (Observer) Head of Planning and Governance (Observer) Inspector – Observer for Induction Inspector – Observer for Induction
Specialist Adviser	Professor Julie Steffan	
Legal Adviser	Tom Rider	Field Fisher 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:

- 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 including impact statement
- Peer Review
- PR response to peer review and confirmation of genetic laboratory accreditation status.
- Written advice from Statutory Approvals Committee Specialist Adviser
- Person Responsible response to written advice from Statutory Approvals Committee Specialist Adviser
- SAC minutes: 24 May 2018 – M0007

1. Consideration of application

1.1. The committee welcomed the advice of its Specialist Adviser, Professor Julie Steffan, who confirmed that the condition was as described in the papers.

1.2. The committee noted that the description in the application for Leber Hereditary Optic Neuropathy (LHON), caused by a mutation in the MT-ND4 gene (m. 11778 G>A) is consistent with the peer review.

Administrative requirements

Application

1.3. 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 Leber Hereditary Optic Neuropathy (LHON), caused by a mutation in the MT-ND4 gene (m. 11778 G>A), 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 Peer Reviewer supported the centre's view that PGD would be unsuitable for this patient. Due to the homoplasmic nature of this gene mutation, a woman harbouring this pathogenic mutation will transmit the variant to all of her off-spring.

Specialist Advice

1.8. The committee noted that the Specialist Adviser to the committee also supported the centre's view that PGD would be unsuitable for this patient as this patient is homoplasmic for this mutation.

1.9. The Specialist Adviser confirmed that males are at a higher risk of being affected (50%) than females (10-20%).

1.10. The committee noted that PGD based on sex selection had been proposed as a means to reduce the risk of having an affected child and discussed this possibility. However, on the advice of its Specialist Adviser, the committee concluded that sex selection would not eliminate the risk completely, as females still have a 10-20% chance of being affected.

Particular Risk

1.11. 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 named woman may have mitochondrial abnormalities caused by mtDNA.

1.12. The committee noted that the application sets out information about LHON, caused by a mutation in the MT-ND4 gene (m. 11778 G>A), including the patient's clinical history and family history of affected individuals, the mutation load and clinical manifestations of the disease.

1.13. The committee noted that this patient is asymptomatic, however remains at life time risk. A relative of the patient manifests clinically. The patient has no preceding pregnancy history and has concerns about the potential risk of passing on a serious mitochondrial disease to her off-spring.

1.14. The committee considered that the patient 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.

Significance and seriousness

1.15. The application describes that LHON mutations are typically homoplasmic, as in this case, and demonstrate incomplete penetrance.

1.16. LHON is the most common form of mitochondrial disease and results in often devastating visual loss. Individuals present with acute/subacute, bilateral, painless, visual loss often in early adult life. Men are four to five times more often affected than women. The spectrum of visual loss may vary with some individuals registered legally blind. Patients who develop visual impairment may be profoundly affected with a major impact on their mental, social and economic well-being. There is emerging evidence to suggest more widespread multi-system involvement in 11778G>A-related LHON including; cardiac arrhythmia, cardiomyopathy and additional neurological features such as progressive global dystonia [muscle spasms and contractions] and a multiple sclerosis (MS)-like illness referred to as Harding-disease. While the co-occurrence of MS and LHON may be due to chance, Harding Disease has a more aggressive course.

1.17. Although visual loss does not characteristically progress after the acute disease phase, the time of impairment (i.e. acute phase of the disease) could have a strong negative impact on the quality of life.

1.18. The impact of the emerging evidence of more widespread multi-system involvement was also considered by the committee. Those with more widespread multi-system involvement including cardiac and extra neurological manifestations such as progressive dystonia (muscle spasms and contractions) and a MS-like illness (that has a more aggressive course) have a considerably greater disease burden which could impact on health-related quality of life.

Peer Reviewer & Specialist Advice

1.19. The Peer Reviewer and Specialist Adviser were supportive of the application for Pronuclear Transfer (PNT) for Leber Hereditary Optic Neuropathy (LHON), caused by a mutation in the MT-ND4 gene (m. 11778 G>A).

Legal Advice

1.20. 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.

1.21. 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)

1.22. 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

1.23. 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

1.24. 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 Leber Hereditary Optic Neuropathy (LHON), caused by a mutation in the MT-ND4 gene (m. 11778 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 that PGD would not be suitable in this case.

Particular Risk

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.

Significant Risk

2.4. 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.

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 & Specialist Advice

2.6. The committee considered the information provided by the centre. The committee also considered advice from the Peer Reviewer and the Specialist 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 Leber Hereditary Optic Neuropathy (LHON), caused by a mutation in the MT-ND4 gene (m. 11778 G>A), 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 also had regard to the patient and the progressive nature of this condition, which may affect her health in the future. The committee acknowledged that the centre is responsible for providing the patient with relevant information concerning her treatment to make fully informed ongoing decisions.

Follow up to mitochondrial donation

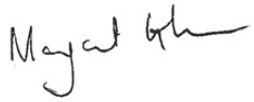
2.13. The committee noted that, to have secured the express provision to enable the centre to undertake PNT, documented processes had to be in place at the centre, setting out how children born from mitochondrial donation will be followed up, where consent has been given. This includes long-term medical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

2.14. 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. Chair's signature

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

Signature



Name

Margaret Gilmore

Date

25 February 2019