Statutory Approvals Committee - minutes

Centre 0017 (Newcastle Fertility Centre at Life)

Mitochondrial Donation using Pronuclear Transfer (PNT) for a specified patient to avoid Leber Hereditary Optic Neuropathy (LHON), OMIM #535000 *516003

Application Reference: M0025

Date:	29 July 2021
Venue:	HFEA, 2nd Floor, 2 Redman Place, London E20 1JQ via Teams Meeting
Committee Members:	Margaret Gilmore (Chair) Emma Cave Anne Lampe Ruth Wilde
Specialist Adviser:	Shamima Rahman
Legal Adviser:	Sarah Ellson, FieldFisher LLP
Members of the Executive:	Moya Berry - Committee officer Catherine Burwood – Licensing Manager
Apologies:	No apologies were received for the meeting
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
- 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 Statutory Approvals Committee (SAC) adviser
- Academic paper referenced by the SAC adviser:
  - Newman et al 2020
- Person Responsible response to written advice
- Further information from the SAC adviser in response to a request form the HFEA Inspector
- Academic papers reference by the SAC adviser:
  - Vignal -Clermont et al 2021
  - Bouquet et al 2019
  - Yu-Mai-Man et al 2020

1. Consideration of application

1.1. The committee welcomed the advice of its expert adviser, Shamima Rahman, 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 Leber Hereditary Optic Neuropathy (LHON), OMIM #535000, *516003 caused by a mutation in the *MT-ND4* gene, 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 Leber Hereditary Optic Neuropathy (LHON), OMIM #535000, *516003 caused by a mutation in the *MT-ND4* 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 Testing for Monogenic disorders (**PGT-M**) –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 Pre-Implantation Genetic Testing for Monogenic Disorders (PGT-M) inappropriate or likely to be unsuccessful.

Peer Review Advice

1.7. The committee noted that the application has been reviewed by the peer reviewer who is supportive of the application, describing the inappropriateness of the use of PGT-M in this case. The peer reviewer is of the view, that as the patient is reported to be homoplasmic for the mutation, the possibility of obtaining an embryo which is also suitable for transfer, appears unlikely and hence, PGT-M treatment is unlikely to be successful for this patient. Therefore, PNT provides the only means of reducing the risk of serious mitochondrial disease in biologically related children born to this woman.

Expert Advice

1.8. The committee noted the advice of the expert adviser who confirmed the patient is reported to be homoplasmic for a variant in the *MT-ND4* gene that is associated with Leber Hereditary Optic Neuropathy (LHON), OMIM #535000, *516003, and that PGM-T would be unsuitable for this patient.

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 mutant mtDNA**.**

1.10. The committee noted that the application sets out information about LHON, caused by a mutation in the *MT-ND4* gene, which includes the patient's clinical history and family history of affected individuals, the mutation load, and clinical manifestations of the disease.

1.11. The committee noted information regarding the observed disease expression within the family pedigree and the effect the disease has had on the patient and close family members.

1.12. The committee considered that the patient has a clearly identified pathogenic mutation which gives rise to considerable risk of any children having serious mitochondrial disease. The details of the factors underlying this rationale have been omitted to protect the identity of the patient.

Significance and Seriousness

1.13. The application describes that Leber Hereditary Optic Neuropathy (LHON), OMIM #535000, *516003 caused by a mutation in the MT-ND4 gene, demonstrates incomplete penetrance. In this case the pathogenic gene mutation has been detected at homoplasmic levels.

1.14. LHON is the most common form of mitochondrial disease and results in often devastating inherited visual loss during young adult life. The mutation that this patient harbours is associated with profound visual loss and may be associated with a multiple sclerosis (MS)-like

illness. Men are four to five times more likely to be affected than women. Affected individuals often present with monocular visual blurring, followed by the insidious onset of similar symptoms in the other eye, on average 2-3 months later. In more than a quarter of cases, visual loss occurs in both eyes simultaneously.

1.15. Although visual loss does not characteristically progress after the acute disease phase, the sudden onset in young adult life can have strong negative impact on quality of life. The severity of negative impact on quality of life has been shown to be worse than in any other form of ophthalmologic disorders previously assessed. Those with more widespread multisystem involvement including cardiac and extra neurological manifestations such as progressive dystonia (muscle spasms and contractions) and an MS-like illness (that has a more aggressive course) have a considerably greater disease burden and impact on health-related quality of life

Peer Reviewer and Expert Advice

1.16. The committee noted the peer review which was supportive of the application and the advice of the expert adviser.

1.17. There is currently no effective treatment for LHON, and treatment is mainly supportive. Although Idebenone can have beneficial effects in preventing further vision impairment and promoting some vision recovery in patients with LHON, it does not lead to clinical recovery in most patients.

1.18. The peer reviewer provided further information regarding gene therapy, stating that trials using adeno-associated virus vectors have been reported in France. Evaluation of the trial data by the EMA is not due to be concluded until 2022 and therefore at present, it is currently not possible to draw conclusions about the efficacy of this treatment.

1.19. The expert adviser confirmed the advice of the peer reviewer, that PGT-M would be inappropriate (as this is a homoplasmic variant), and that sufficient information has been provided to make an assessment of the significance of the risk.

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 a preventative strategy for patients with a severe mitochondrial disease caused by a pathogenic mtDNA variant 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 variants

known to 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 (known as "reversion") 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), OMIM #535000, *516003 caused by a mutation in the *MT-ND4* gene, 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 Testing for Monogenic disorders (PGT-M) – Patient Selection Criteria

2.2. The committee considered the advice presented in the application by the peer reviewer and the expert adviser and agreed that PGT-M 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 an 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 medical and family history, which included a statement from the patient and an affected relative, detailing the devastating impact of the disease. The information indicates that any child conceived by her is likely to be at significant risk of being affected physically, psychologically, and socially by this serious disease which could severely impact on their quality of life.

Peer Review and Expert Advice

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

2.7. The committee noted that acquired blindness at a young age is a serious condition which is convincingly described and appreciated by the patient. As the condition can have more wide-spread multi-system involvement, although at low frequency, this makes the worst-case scenario even more serious.

Authorised Treatment

2.8. 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), OMIM #535000, *516003 caused by a mutation in the *MT-ND4* gene, for the patient named in the application. The committee noted the rapid development of the condition, the emerging evidence of multi-system symptoms, and the fact there is no permanent cure. The committee recognised the right of the patient not to be identified.

HFEA Code of Practice

2.9. 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

2.10. The committee emphasises that the centre needs to fulfil the HFEA's counselling requirements for all involved in mitochondrial donation and ensure that patients are provided with relevant information. The committee noted that this would include consideration of the material risks involved to enable patients to make fully informed choices.

2.11. The committee agreed that counselling should be continued to be offered after treatment.

Welfare of the child

2.12. 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.

2.13. The committee also had regard to the patient and her own mitochondrial disease burden. 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 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.

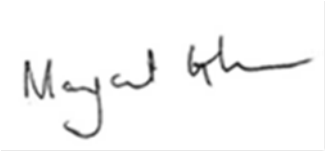
2.15. The committee encouraged the centre to ask for the patient's consent to contact them following mitochondrial donation treatment and should a child be born, to check up on the child's health and development in the future. As this is a new technique, the medical and scientific community needs to 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. Chair's signature

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

Signature



Name

Margaret Gilmore

Date

19 August 2021