Statutory Approvals Committee – minutes

Centre 0017 (Newcastle Fertility Centre at LIFE)

Mitochondrial Donation using Pronuclear Transfer (PNT) Application Reference: M0021 to avoid Leber Hereditary Optic Neuropathy (LHON), OMIM #516000, *535000 caused by a mutation in the MT-ND1 gene.

Thursday, 25 June 2020

HFEA, 10 Spring Gardens, London, SW1A 2BU via Teleconference

Committee members	Margaret Gilmore (Chair) Emma Cave Anne Lampe Ruth Wilde	
Members of the Executive	Moya Berry Catherine Burwood	Committee Officer Licensing Manager
Expert Adviser	Professor Bert Smeets	
Legal Adviser	Ros Foster	Browne Jacobson - LLP

Declarations of interest:

- Members of the committee declared that they had no conflicts of interest in relation to this item.

Apologies:

- Apologies were received from Tony Rutherford.

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
- Person Responsible response to peer review
- Written advice of 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 Bert Smeets, 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 #516000, *535000 caused by a mutation in the MT-ND1 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 #516000, *535000 caused by a mutation in the MT-ND1 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 who is supportive of the application, describing the inappropriateness of the use of PGD in this case. As the patient is reported to be almost homoplasmic for the mutation, it is unlikely that a suitable embryo would be obtained for PGD. Therefore, Mitochondrial replacement therapy (MRT) provides the only means of reducing the risk of serious mitochondrial disease in children born to this woman.

Expert Advice

1.8. The committee noted the advice of the expert adviser who confirmed the patient is near homoplasmic for the Leber Hereditary Optic Neuropathy (LHON), OMIM #516000, *535000 caused by a mutation in the MT-ND1 gene. Therefore, the expert adviser is of the view that PGD would not be suitable, as all PGD embryos would be homoplasmic or have a very high mutation load above the level of expression, placing any child conceived naturally, at a significant risk of developing a serious mitochondrial disease.

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 LHON, caused by a mutation in the MT-ND1 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 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 LHON mutations are typically homoplasmic/highly heteroplasmic and demonstrate incomplete penetrance and variable expression. In this case the pathogenic mutation has been detected at nearly homoplasmic levels in this patient's samples and the patient’s mutant mitochondrial load is above the threshold level for clinical manifestations.

1.14. LHON is the most common form of mitochondrial disease and results in often devastating inherited visual loss. Individuals frequently present with acute/subacute, bilateral, painless visual loss often in early adult life. Men are four to five times more likely to be affected than women. Visual loss does not characteristically progress after the acute disease phase. The spectrum of visual loss may vary, with some individuals being registered as legally blind. Most patients who develop visual impairment are profoundly affected with a major impact on their mental, social, and economic well-being.

1.15. The rate of progression of symptoms is variable but it may be only a few months from the onset of symptoms to severe visual impairment. While in the vast majority of cases, clinical features are limited to the eye, there is some emerging evidence to suggest that, in rare cases, it may be associated with extra-ocular, multi-system features. These include cardiomyopathy and extra neurological features including progressive 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 appears to have a more aggressive course.

Peer Reviewer & Expert Advice

1.16. The expert adviser was supportive of the application for Pronuclear Transfer (PNT) for Leber Hereditary Optic Neuropathy (LHON), OMIM #516000, *535000 caused by a mutation in the MT-ND1 gene. In the opinion of the expert adviser, acquired blindness at a young age is a serious

condition as described by the patient's relative, and appreciated by the patient. As the condition can have more widespread multi-system involvement, although at low frequency, this makes the worst-case scenario even more serious. Although Idebenone can have beneficial effects in preventing further vision impairment and promoting vision recovery in patients with LHON, it does not lead to clinical recovery in most patients.

1.17. The peer reviewer was also supportive of the application.

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

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 #516000, *535000 caused by a mutation in the MT-ND1 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 Diagnosis (PGD) - 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 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 medical and family history, which included a statement from the patient, 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 the quality of life.

Peer Review & 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. The committee noted the advice of the expert adviser, and in particular 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

2.7. 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), OMIM #516000, *535000 caused by a mutation in the MT-ND1 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

2.8. 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 ensure that patients are provided with relevant 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 as well as the late onset 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

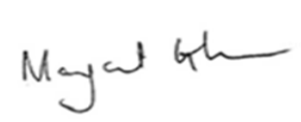
2.13. The committee noted that, to have secured the express provision to enable the centre to undertake PNT, documented processes had to be in place at the centre, setting out how children born from mitochondrial donation will be followed up, where consent has been given. This includes long-term medical 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. Chairs signature

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

Signature



Name
Margaret Gilmore

Date
23 July 2020