Statutory Approvals Committee – minutes

Centre 0017 (Newcastle Fertility Centre at LIFE)

Mitochondrial Donation using Pronuclear Transfer (PNT) Application Reference: M0011 to avoid Leber Hereditary Optic Neuropathy (LHON), OMIM #535000, caused by a mutation in the MT-ND4 gene (m.11778 G>A)

Thursday, 29 August 2019

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

Committee members	Margaret Gilmore (Chair) Bobbie Farsides (Deputy Chair) Anne Lampe	
Members of the Executive	Moya Berry Catherine Burwood	Committee Secretary Licensing Manager (Observer)
Expert Adviser	Professor Bert Smeets	
Legal Adviser	Dawn Brathwaite	Mills & Reeve LLP
Observer	Darryn Hale	DAC Beachcroft LLP

Declarations of interest

- Members of the committee declared that they had no conflicts of interest in relation to this item.
- Apologies were received from Rachel Cutting and 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

Part 1 – original application

- Executive summary
- Application form
- Peer review form
- PR response to peer review
- Figure to accompany PR response to peer review
- Peer review response to rebuttal
- Written advice of SAC adviser
- PR response to written advice
- SAC minutes: 24 May 2018 – M0007
- SAC minutes: 25 October 2018 – M0011

Part 2 – update to committee

- Letter from PR – reapplication of M0011
- Response to appeal letter from peer reviewer
- SAC adviser's written comments
- PR's response to SAC adviser's written comments – letter
- PR's response to SAC adviser's written comments – appendix
- SAC advisors request for further information
- PR's response to SAC adviser's request
- SAC advisors second request for further information
- PR's response to SAC adviser's second request
- PR's response to SAC adviser's second request - additional figure
- Final written advice from SAC adviser

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 following its meeting on the 25 October 2018, it had decided to adjourn the decision on whether to allow mitochondrial donation (PNT) treatment for this condition pending further information to assess whether PGD could provide the couple in question with a healthy child. This information has now been provided by the centre to address the points raised by the committee and an updated application submitted.

1.3. 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, caused by a mutation in the MT-ND4 gene (m.11778 G>A) is consistent with the peer review.

Administrative requirements

Application

1.4. 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), 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

1.5. 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 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

1.7. 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

1.8. The committee noted that the application has been reviewed by the peer reviewer. The reviewer did not initially consider enough information was available to make an assessment on the significance of the risk, as the application did not explicitly state the recurrence risks of the known links to smoking. The peer reviewer did not, on the application as first presented, agree that PGD would be inappropriate in this case, stating that there was a significant chance that some oocytes would have less than 60% of the m.11778A>G mutation and be low risk of developing the disorder.

1.9. The committee noted that the person responsible (PR) addressed the points raised by the peer reviewer and the information had been returned to the clinical expert for their final response.

1.10. Based on the additional information provided by the centre, the peer reviewer is now of the view that PGD would be unsuitable for this patient.

Expert Advice

1.11. The expert adviser initially stated that the application did not contain enough information to conclude whether PGD would be inappropriate and outlined some important factors necessary to make a determination. Based on the additional information provided by the centre, the expert adviser now supports the centre's view that PGD would be unsuitable for this patient, for the m.11778G>A in MT-ND4 (LHON) mutation in her germ line.

1.12. The patient is highly heteroplasmic for the Leber Hereditary Optic Neuropathy (LHON), caused by a mutation in the MT-ND4 gene (m. 11778 G>A). The expert adviser confirmed the additional information provided by the centre had been reviewed to assess the applicability of PGD for this case and an evaluation of evidence relating to three specific issues was discussed. These related to:

- Threshold of expression.
- The percentage of embryos that would be below the threshold of expression.
- Whether the patient would produce sufficient oocytes per IVF cycle to select an embryo below the threshold.

Particular Risk

1.13. 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.

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

1.15. The committee noted that to date the patient is asymptomatic but remains at an increased life-time risk of developing symptoms of mitochondrial disease due to the nature of these mutations. 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.

1.16. 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

1.17. The application describes that LHON mutations are typically homoplasmic/high heteroplasmic, as in this case, and demonstrates incomplete penetrance. The committee acknowledged the helpfulness of the 'family tree' diagram in clearly outlining the significance and seriousness of the disease.

1.18. LHON is the most common form of mitochondrial disease and often results in 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.

1.19. Although visual loss does not characteristically progress after the acute disease phase, the time of impairment (i.e. acute phase of the disease) and onset in early adulthood could have a strong negative impact on the quality of life. The severity of negative impact on quality of life has been shown to be worse than in any other forms of ophthalmologic disorders.

1.20. 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 & Expert Advice

1.21. The expert adviser was 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). The peer reviewer was also supportive of the application.

Legal Advice

1.22. 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.

1.23. 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)

1.24. 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

1.25. 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

1.26. 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 noted its initial decision in October 2018 to adjourn the application of mitochondrial donation treatment (PNT) for this patient pending further detailed information relating to three specific issues; threshold of expression, the percentage of embryos that would be below the threshold of expression and whether the patient would produce sufficient oocytes per IVF cycle to select an embryo below the threshold.

2.3. The committee thanked the centre for providing this additional detailed data and acknowledged the time and commitment of the centre to provide this information, which has enabled the committee to reach a fair and legally acceptable decision based on scientific facts.

2.4. The committee considered the advice presented in the updated application and agreed that PGD would not be suitable in this case.

Particular Risk

2.5. 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

2.6. 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.

2.7. 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

2.8. 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

2.9. 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

2.10. 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

2.11. 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.

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

Welfare of a child

2.13. 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.

2.14. 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

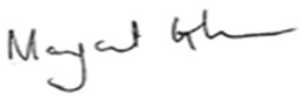
2.15. The committee noted that, to have secured the express provision to enable the centre to undertake PNT, documented processes had to be in place at the centre, setting out how children born from mitochondrial donation will be followed up, where consent has been given. This includes long-term medical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

2.16. 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
16 September 2019