Statutory Approvals Committee – minutes

Centre 0017 (Newcastle Fertility Centre at LIFE)

Mitochondrial Donation using Pronuclear Transfer (PNT) Application Reference: M0018 to avoid the inheritance of mitochondrial disease, OMIM #540000 and #520000, caused by MT-TL1 gene mutation.

Thursday, 26 March 2020

HFEA Teleconference Meeting

Committee members	Margaret Gilmore (Chair) Emma Cave Anne Lampe Tony Rutherford Ruth Wilde	
Members of the Executive	Moya Berry Catherine Burwood	Committee Officer Licensing Manager
Expert Adviser	Professor Julie Steffann	
Legal Adviser	Gerard Hanratty	Browne Jacobson - LLP

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 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 mitochondrial disease, OMIM #540000 and #520000, caused by a mutation in the MT-TL1 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) to avoid the inheritance of related mitochondrial disease, OMIM #540000 and #520000, caused by a mutation in the MT-TL1 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 Reviewer 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. Given the high levels of mutant mtDNA that the patient harbours and the expression of disease within the family pedigree, the patient is considered at significant risk of developing additional symptoms of the disease over her life span. It was also noted that the patient had undergone a cycle of PGD which produced 6 embryos, none of which could be replaced because of the MtDNA heteroplasmy.

Expert Advice

1.8. The committee noted the advice of the expert adviser who confirmed that the patient is heteroplasmic for this mitochondrial disease, OMIM #540000 and #520000, caused by MT-TL1 gene mutation and is known to harbour a significantly high level of mutant mtDNA. Therefore, the expert adviser, based on the evidence provided, was of the view that PGD would not be suitable. The expert adviser confirmed that all PGD embryos would be heteroplasmic and have a significant risk of being affected, well above the recognised threshold for clinical manifestation of serious mtDNA 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 the Mitochondrial DNA (mtDNA) mutations, OMIM #540000 and #520000, caused by MT-TL1 gene mutation 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 was satisfied on the evidence before it, that the patient is at a life-time risk of developing additional symptoms of mitochondrial disease due to the nature of the mutation. The committee noted that the patient is symptomatic with a moderate degree of disease burden. The committee was satisfied on the evidence before it and the expression of disease within the family pedigree, that the patient is at risk of developing further symptoms of mitochondrial disease over the period of her lifespan.

1.12. The committee noted 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 MT-TL1 gene mutations as being typically heteroplasmic and demonstrate incomplete penetrance and variable expression. In this case the pathogenic MT-TL1 gene mutation has been detected at heteroplasmic levels significantly above the threshold level for clinical manifestations.

1.14. The mutation in MT-TL1 is recognised to give rise to several clinical symptoms including chronic progressive external ophthalmoplegia, MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke) and MIDD (maternally inherited diabetes and deafness).

1.15. MELAS syndrome is often a devastating, progressive, neurodegenerative disorder, impacting considerably on quality of life and long-term survival. In severe forms of the disease, patients require the use of a wheelchair, due to disabling myoclonus [spasmodic contraction of muscles] and ataxia [loss of full control of bodily movements], and often require assistance with all activities of daily living, including eating, washing and dressing. Patients may also develop other symptoms including intractable seizures, encephalopathy, recurrent stroke-like episodes, progressive

cognitive impairment resulting in dementia, diabetes, deafness, neuropathy, gastro-intestinal dysmotility (including intestinal pseudo-obstruction) and cardiac complications (including arrhythmias, cardiomyopathy and sudden death syndrome). In the later stages of the disease, patients often require regular hospital admissions for management of stroke-like episodes, seizures, encephalopathy, urinary tract infections (including management of urinary obstruction), aspiration pneumonia (resulting from chronic immobility, swallowing and speech dysfunction and abnormal emptying of stomach) and bowel management that often mimics an acute surgical abdomen (resulting from chronic intestinal dysmotility). In addition, psychiatric symptoms are prominent cogent to the relentlessly progressive nature of the dementing process, precipitating acute hospital admissions for management of behavioural and cognitive issues that are often resistant to conventional anti-psychosis pharmacological agents.

Peer Reviewer and Expert Advice

1.16. The expert adviser was supportive of the application for Pronuclear Transfer (PNT) for this MT-TL1 gene mutation. In the opinion of the expert adviser and on the evidence provided, the patient is considered not only to be at risk of developing further symptoms of the condition but is at high risk of transmitting the mtDNA mutation to future offspring as evident from a previous cycle of PGD. The centre therefore must ensure the patient is adequately counselled as to her own risks, and she should receive comprehensive screening for additional risk factors or contraindications for pregnancy.

1.17. The peer reviewer was also supportive of the application, stating that, in an individual with this mtDNA mutation, PGD was inappropriate and likely to be unsuccessful.

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 these applications were 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 this MT-TL1 gene mutation, OMIM #540000 and #520000 is conditional on the embryo subsequently being created by the fertilisation of an egg extracted from the ovaries of the woman so named, Regulation 8(b).

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

2.2. The committee considered the advice presented in the application 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 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 because the patient carries very high mutant loads, she is considered at high risk to transmit the mutation at high mutant levels.

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 OMIM #540000, #520000 caused by the MT-TL1 gene mutation, for the patient named in the application. The committee noted the progressive and devastating nature of the condition which often presents from childhood, the emerging evidence of multi-system symptoms, and the fact there is no 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 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.

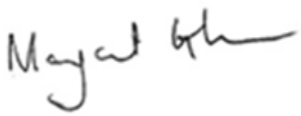
Follow up to mitochondrial donation

2.13. The committee 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



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Date
23 April 2020