Statutory Approvals Committee – minutes

Centre 0017 (Newcastle Fertility Centre at LIFE)
Mitochondrial Donation using Pronuclear Transfer (PNT)
Application Reference: M0010
Homoplasmic mitochondrial mutation in the MT-TI gene (4300A>G)

Thursday, 27 September 2018

HFEA, 10 Spring Gardens, London, SW1A 2BU

Committee members	Margaret Gilmore (Chair) Bobbie Farsides (Deputy Chair) Ruth Wilde	
Members of the Executive	Dee Knoyle Bernice Ash Catherine Burwood Paula Robinson	Committee Secretary Committee Secretary (Observer) Senior Governance Manager Head of Planning and Governance (Observer)
Specialist Adviser	Professor Peter Braude	
Legal Adviser	Dawn Brathwaite	Mills & Reeve 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:

- 8th 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 patient and relative statement)
- Peer Review
- PR response to Peer Review
- Family Pedigree included in PR response to Peer Review
- Written advice from Statutory Approvals Committee Specialist Adviser
- Person Responsible response to written advice from Statutory Approvals Committee Specialist Adviser

1. Consideration of application

1.1. The committee welcomed the advice of its Specialist Adviser, Professor Peter Braude, who confirmed that the condition was as described in the papers, emphasising that the condition could present with a sudden appearance or worsening of symptoms that could lead to cardiac failure, rather than there being a risk of sudden cardiac death seen in some other genetic disorders.

1.2. The committee noted that the description in the application for Homoplasmic mitochondrial mutation in the MT-TI gene (4300A>G) is consistent with the peer review.

1.3. The committee had regard to its decision tree.

Administrative requirements

Application

1.4. 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 Homoplasmic mitochondrial mutation in the MT-TI gene (4300A>G), 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.

Significance and seriousness

1.7. Mitochondrial cardiomyopathy can be described as a myocardial condition characterised by abnormal heart-muscle structure, function, or both, secondary to genetic defects involving the mitochondrial respiratory chain, in the absence of concomitant coronary artery disease, hypertension, valvular disease, or congenital heart disease. The clinical features of this form of cardiomyopathy are distinct from other genetic forms of hypertrophic obstructive cardiomyopathy (HOCM - thickening of the heart muscle) often presenting with non-obstructive HOCM without symptoms of other system involvement.

1.8. The committee noted that mitochondrial cardiomyopathy is often a devastating, progressive, disorder impacting considerably on quality of life and long-term survival. The illness frequently presents with a sudden onset of symptoms with rapidly evolving cardiac failure. The disease course is often progressive, with left ventricular dilation and cardiac failure, even at a young age. Adverse clinical outcomes, include heart failure necessitating cardiac transplantation, high morbidity and early mortality (with childhood deaths reported). Evolution of cardiac features may manifest across the life span.

1.9. 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.

Particular Risk

1.10. 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 a named woman may have mitochondrial abnormalities caused by mtDNA.

1.11. The committee noted that the application sets out information about Homoplasmic mitochondrial mutation in the MT-TI gene (4300A>G), including the patient's clinical history and family history of affected individuals, their mutation load and clinical manifestations of the disease.

1.12. 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.

1.13. The committee noted that this patient is currently asymptomatic but remains at life-time risk of developing symptoms of mitochondrial cardiomyopathy due to the nature of these mutations. This patient remains under regular cardiac surveillance.

1.14. 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. While the mutation is associated with maternally inherited hypertrophic obstructive cardiomyopathy, it is reported to show variable expression. Hence, the mutant load does not correlate with clinical symptoms. The presence of this pathogenic mutation does not predict disease occurrence, age of onset, disease severity or rate of progression. The variable age and severity of the disorder in this family is well documented in the genetic tree that was presented in the additional papers.

Patient selection criteria

Pre-implantation Genetic Diagnosis (PGD) considered

1.15. 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.

1.16. The committee noted that the Peer Reviewer supported the centre’s view that PGD would be unsuitable for this patient.

1.17. 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.

Mitochondrial Donation using Pronuclear Transfer (PNT)

1.18. 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 the condition onto 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

1.19. 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

1.20. 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 Homoplasmic mitochondrial mutation in the MT-TI gene (4300A>G) 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.

Significant Risk

2.3. On the basis of the information presented, the committee was 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.

2.4. 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 life threatening, progressive disease which severely impacts the quality of life.

Particular Risk

2.5. On the basis of the information presented, the committee was also 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.

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 Homoplasmic mitochondrial mutation in the MT-TI gene (4300A>G), 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 further 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

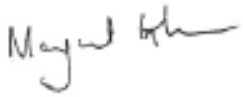
2.13. The committee noted that, to have secured the express provision to enable the centre to undertake PNT, documented processes had to be in place at the centre, setting out how children born from mitochondrial donation will be followed up, where consent has been given. This includes long-term medical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

22 October 2018