Statutory Approvals Committee – minutes

Centre 0037 (Glasgow Royal Infirmary)
Pre-implantation Genetic Diagnosis (PGD) application for Familial Partial Lipodystrophy Type 3, OMIM #604367

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	Bernice Ash Dee Knoyle Paula Robinson Catherine Burwood	Committee Secretary Committee Secretary (Observer) Head of Planning and Governance (Observer) Senior Governance Manager (Observer)
Specialist Adviser	Professor Peter Turnpenny	
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.

The following papers were considered by the committee:

- Executive Summary
- PGD Application Form
- Redacted Peer Review
- Genetic Alliance UK statement
- Licence committee minutes, 9 July 2007, PGD for Partial lipodystrophy, familial, type 2, centre 0102

1. Consideration of application

1.1. The committee welcomed the advice of its Specialist Adviser, Professor Peter Turnpenny who confirmed that the condition was as described in the papers.

1.2. The committee noted that the description in the application for PGD for Familial Partial Lipodystrophy Type 3, OMIM #604367 is consistent with the peer review.

1.3. The committee noted that the Genetic Alliance opinion provided a patient perspective and supported the application.

1.4. The committee had regard to its decision tree. The committee noted that the centre is licensed to carry out PGD. The committee was also satisfied that the centre has experience of carrying out PGD and that generic patient information about its PGD programme and associated consent forms had previously been received by the HFEA.

1.5. The committee noted that the condition being applied for is not on the list of approved PGD conditions.

1.6. The committee noted that the proposed purpose of testing the embryos was as set out in paragraph 1ZA(1)(b) of Schedule 2 of the Act, i.e. 'where there is a particular risk that the embryo may have any gene, chromosome or mitochondrion abnormality, establishing whether it has that abnormality or any other gene, chromosome or mitochondrion abnormality'.

1.7. The committee noted that as information was not included in the application form, the Peer Reviewer had clarified that the condition is inherited in an autosomal dominant pattern which means there is a 50% chance of an embryo being affected with the condition in each pregnancy, if either parent has a relevant mutation.

1.8. The Familial Partial Lipodystrophies are genetic disorders of which six types have been described, five of which have known genetic causes. This application is for FPLD3, which is caused by a mutation in the *PPARG* gene. FPLD3 is characterised by both partial lipodystrophy and metabolic disturbances, the latter being more prominent than the former.

1.9. The committee noted that in FPLD3, lipodystrophy often commences during puberty and includes selective, progressive loss of subcutaneous fat from various areas of the body, including the limbs and gluteal regions, and abnormal accumulation of fat around the abdomen. Metabolic disturbances include insulin resistance, early onset diabetes (mean age of onset 31 years; range 8 – 53 years) and an inability to properly metabolise glucose leading to elevated levels of triglycerides in the blood and low HDL cholesterol levels. Women tend to experience more severe metabolic consequences than men due to having significantly more body fat under heathy circumstances (1.5 to 2-fold more). Women can also go on to develop polycystic ovary syndrome (PCOS) after puberty, resulting in menstrual irregularity, hirsutism and potential fertility difficulties. The metabolic disturbances in patients with FPLD3 often lead to early onset hypertension, coronary artery disease, cardiomyopathy, fatty liver disease and pancreatitis. Age of onset and clinical phenotype is very variable within families. Penetrance figures are unknown but in the few published pedigrees, penetrance is high. Body image can be affected as patients experience disproportionate fat distribution and hirsutism.

1.10. FPLD3 is incurable, but symptoms can be managed. Diabetes can sometimes be controlled through dietary restriction along with taking metformin, Glucagon-like peptide-1 (GLP1), and insulin. Leptin has been tried in patients with very low leptin levels. The PPARG agonist thiazolidinediones (TZDs) have been trialled in some patients to improve tissue sensitivity to insulin but clinical use of TZDs has been limited by the occurrence of fluid retention and heart failure in 15% of patients. Hypertension can also be managed using medication. Despite treatment however, patients may still suffer from diabetes and hypertension associated complications and the combination of diabetes, hypertension and dyslipidaemia has the potential to cause long term serious health problems.

1.11. The committee noted that Familial Partial Lipodystrophy Type 2 (FPLD2) OMIM #151660 has been on the approved PGD condition list since July 2007, acknowledging the minutes included in the papers. This condition is inherited in an autosomal dominant fashion and results in a similar phenotype to FPLD3, with patients experiencing abnormal fat distribution from around the age of puberty, insulin resistance, diabetes and menstrual disorder for female patients.

1.12. The Peer Reviewer noted that there are currently 6 known subtypes of Familial Partial Lipodystrophy and that "the responsible genes have been identified in types 2 [FPLD2, OMIM #151660], 4 [FPLD4, OMIM #613877], 5 [FPLD5 OMIM #615238] and 6 [FPLD6, OMIM #615980] as well as type 3 [FPLD3]". They clarify that FPLD2 is caused by a mutation in the *LMNA* gene and FPLD4 by mutation in the *PLIN1* gene; both FPLD2 and 4 are inherited in an autosomal dominant fashion. FPLD5 is caused by mutation in the *CIDEC* gene and FPLD6 by mutation in the *LIPE* gene; both FPLD5 and 6 are inherited in an autosomal recessive fashion. The committee noted there is no recommendation as to whether these additional FPLD types should be included with this application.

1.13. The Executive had reviewed the OMIM website for the symptoms of FPLD 2-6. This showed that partial lipodystrophy, metabolic and endocrine disturbances (involving dyslipidaemia, insulin resistance, and diabetes mellitus) and hepatic steatosis, are seen in FPLD types 2-6. Hypertension is seen in FPLD 2,3 and 4. Pancreatitis can be seen in FPLD2 and 5. PCOS and hirsutism are only seen in FPLD2 and 3. The Executive also noted that according to the OMIM website, FPLD5 has only been characterised in one family.

1.14. The committee welcomed the advice of the Specialist Adviser, who clarified that FPLD types 3 and 4 are very similar. As previously stated, FPLD types 5 and 6 are inherited in an autosomal recessive manner. The Specialist Adviser confirmed that type 5 had only been identified in one family, but type 6 had been characterised in more than one group.

1.15. The committee noted the inspectorate's request to consider whether Familial Partial Lipodystrophy Type 3, OMIM #604367 should be approved for inclusion on the PGD List. Thereafter, the committee was also asked to consider the Peer Reviewer's comments on the additional types of FPLD, which are not yet approved. The committee agreed to consider the application on this basis.

2. Decision

2.1. The committee considered that, in the worst case scenario, Familial Partial Lipodystrophy Type 3, OMIM #604367 is serious as the condition has an early onset, is complex, multi-symptomatic and can be life threatening. The condition severely impacts on the individual's quality of life and the family.

2.2. The committee proceeded to consider the inspectorate's request to consider whether Familial Partial Lipodystrophy types 4-6 should be added to the list of conditions for which PGD can be applied. The committee considered that types 4 and 6 are, in the worst case scenario, serious conditions, in the same manner as Familial Partial Lipodystrophy Type 3, OMIM #604367, having a severe impact on the individual and are multi-symptomatic.

2.3. The committee considered that, due to Familial Partial Lipodystrophy Type 5 only known to be characterised in one family, not to approve this condition for licensing for PGD at this time.

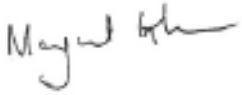
2.4. The committee had regard to its explanatory note and confirmed that, on the basis of the information presented, it was satisfied that there is a particular risk that an embryo may have the abnormality in question and that there is a significant risk, given the condition's worst symptoms, that a person with the abnormality will have or develop a serious physical or mental disability, a serious illness or any other serious medical condition. The committee was therefore satisfied that the following conditions meet the criteria for testing under paragraph 1ZA(1)(b) and (2) of Schedule 2 of the Act and agreed to authorise testing:

- Familial Partial Lipodystrophy Type 3, OMIM #604367
- Familial Partial Lipodystrophy Type 4, OMIM #613877
- Familial Partial Lipodystrophy Type 6, OMIM #615980

3. Chairs signature

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

Signature



Name

Margaret Gilmore

Date

22 October 2018