Statutory Approvals Committee – minutes

Centre 0102 (Guy's Hospital)

Pre-implantation Genetic Diagnosis (PGD) application for

Microcephalic Osteodysplastic Primordial Dwarfism Type 1, (MOPD1)

OMIM #210710

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 (Observer) Head of Planning and Governance (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
- Email from centre staff regarding an error in the OMIM number in the initial application and stating to include MOPD types 2 and 3 in the application.

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 Microcephalic Osteodysplastic Primordial Dwarfism Type 1 (MOPD1), OMIM #210710 is consistent with the peer review.

1.3. The committee noted that an incorrect OMIM number (OMIM #210720) was included in the initial application. This number refers to Microcephalic Osteodysplastic Primordial Dwarfism Type 2 (MOPD2), whereas the correct OMIM reference for Microcephalic Osteodysplastic Primordial Dwarfism Type 1 (MOPD1), is OMIM #210710. The applicant has confirmed that the initial application is for (MOPD1), OMIM #210710.

1.4. The Peer Reviewer recommends considering one additional condition which also belongs to the Microcephalic Osteodysplastic Primordial Dwarfism group of disorders, (MOPD2), OMIM #210720, which is caused by homozygous or compound heterozygous mutations in the gene that encodes the protein Pericentrin. As with MOPD1, patients with MOPD2 experience severely affected growth. However, the peer review highlights that with MOPD2 intellectual disability can be much milder and survival longer for example into young adulthood. The peer review also states that approximately one third of affected individuals with MOPD2 appear to develop cerebrovascular disease with resulting ischaemic brain damage and there is no curative treatment for this condition. The centre agreed that it was beneficial to include the consideration of MOPD2 with their original application.

1.5. The centre suggested that it would be beneficial to also consider Microcephalic Osteodysplastic Primordial Dwarfism Type 3 (MOPD3), OMIM #210730, in this application.

1.6. The committee noted that the conditions being applied for are not on the list of conditions approved for PGD.

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

1.8. 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.

1.9. 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'.

1.10. The committee noted that MOPD1 is inherited in an autosomal recessive manner which means there is a 25% chance of having an affected child in each pregnancy, if each parent has a relevant mutation.

1.11. The committee noted that MOPD1 is caused by mutations in the *RNU4ATAC* gene. The condition is characterized by both intrauterine and postnatal grown failure, microcephaly (small head size), skeletal dysplasia (abnormal bone development) and neurologic abnormalities, including intellectual disability and brain malformations. The condition develops prenatally and is evident at birth. Infants and children can have an immune deficiency making them prone to serious infections and death during early childhood. Depending on the degree of limb contractures and neuro-disability, those who survive into childhood may not walk. Speech development may not occur and, due to neuronal migration abnormalities (where the neurons come to lie in abnormal places in the brain), intractable seizures may arise. There are allelic disorders - Roifman syndrome and Lowry-Wood syndrome - which are also caused by mutations in the *RNU4ATAC* gene and result in milder outcomes than MOPD1 in terms of developmental delay. These are not being considered in this application.

1.12. The committee noted that patients with MOPD1 are likely to be very small at birth, with a small head, joint contractures, facial dysmorphism, sparse thin hair, and dry skin; they are all of extreme short stature. They also experience abnormal brain development which can result in profound developmental delay, blindness, hearing deficits, central nervous system malformations, early-onset epilepsy and neuroendocrine dysfunction. Patients are prone to infections at any time from birth due to immunological deficiencies. The classical form of the disorder is associated with profound neuro-disability and frequently death in early childhood. While developmental delay is universal, variability exists. There is some genotype-phenotype correlation with the position of *RNU4ATAC* mutations; however, it is not yet known how marked intra-family variability can be, therefore risk may remain for more severe phenotypes in families with a less severely affected individual. The condition is fully penetrant with most cases being severe. There are rare examples of slightly milder presentation but still with significant disability.

1.13. The committee noted the inspectorate's request to consider whether the following conditions should be approved for inclusion on the list of conditions approved for PGD and the committee agreed to consider the application on this basis:

- Microcephalic Osteodysplastic Primordial Dwarfism Type 1 (MOPD1), OMIM #210710
- Microcephalic Osteodysplastic Primordial Dwarfism Type 2 (MOPD2), OMIM #210720

1.14. The committee noted that according to the OMIM website, a causative gene has not been characterised in MOPD3 and its symptoms vary little from those of MOPD1, since it causes serious life limiting abnormalities in relation to severe growth delay, multiple skeletal abnormalities, moderate to severe developmental delay, renal abnormalities, and death in infancy. The OMIM website at states #210710: 'There is a consensus that the osteodysplastic primordial dwarfism types I and III of Majewski and Goecke (1982) and Majewski et al. (1982) (i.e. MOPD1 and MOPD3) and Taybi-Linder cephaloskeletal dysplasia are variations of the same entity.' Therefore, the Executive suggested that MOPD3 is not considered as an additional condition in this application, subject to the opinion of the Specialist Adviser to the committee.

1.15. The committee agreed that it would not include MOPD3 as an additional condition in this application, as advised by the Executive and the Specialist Adviser.

2. Decision

2.1. The committee considered that, in the worst case scenario MOPD1 and MOPD2 are serious, life-limiting conditions that cause microcephaly, facial dysmorphism, skeletal dysplasia and extreme short stature. The onset of these conditions is prenatal and evident at birth, causing profound neurological abnormalities, brain malformations, seizures which are difficult to treat, and intellectual disability. Children may be blind with hearing impairment, they may not walk and their speech may not develop. These conditions also affect the immune system so individuals are prone to serious infections and death in early childhood. The quality of life for affected individuals is severely impacted and there is no curative treatment.

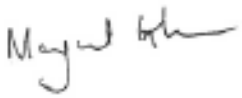
2.2. The committee had regard to its explanatory note and confirmed that, on the basis of the information presented, it was satisfied that there is a particular risk that an embryo may have the abnormality in question and that there is a significant risk, given the condition's worst symptoms, that a 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:

- Microcephalic Osteodysplastic Primordial Dwarfism Type 1, (MOPD1), OMIM #210710
- Microcephalic Osteodysplastic Primordial Dwarfism Type 2, (MOPD2), OMIM #210720

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