Statutory Approvals Committee – minutes

Centre 0102 (Guy's Hospital)

Pre-implantation Genetic Diagnosis (PGD) application for

Multiple Congenital Anomalies Hypotonia-Seizures-Syndrome Type 3 (MCAHS3) OMIM #615398

Thursday, 30 August 2018

HFEA, 10 Spring Gardens, London, SW1A 2BU

Committee members	Margaret Gilmore (Chair) Bobbie Farsides (Deputy Chair) Anne Lampe Ruth Wilde	
Members of the Executive	Bernice Ash Paula Robinson Catherine Burwood	Committee Secretary Head of Planning and Governance (Observer) Senior Governance Manager (Observer)
Specialist Adviser	Dr Alan Fryer	
Legal Adviser	Jane Williams	Mills & Reeve LLP
Observers	Stevan Cirkovic	Policy Officer (Induction)

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
- Email from centre regarding additional subtypes
- Genetic Alliance UK statement
- 2014-01-30 SAC Minutes (Item 5) - PGD for Multiple Congenital abnormalities (OMIM #614080) - Centre 0044

1. Consideration of application

1.1. The committee welcomed the advice of its Specialist Adviser, Dr Alan Fryer, 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 Multiple Congenital Anomalies Hypotonia-Seizures-Syndrome (MCAHS) Type 3 (MCAHS3), OMIM #615398 and Multiple Congenital Anomalies Hypotonia-Seizures-Syndrome Type 2 (MCAHS2), OMIM #300868 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 MCAHS3 is inherited in an autosomal recessive pattern which means there is a 25% chance of an embryo being affected with the condition in each pregnancy, if both parents have a relevant mutation.

1.8. The committee noted that MCAHS2 has an X-linked recessive inheritance pattern which means there is a 25% chance of a male embryo being affected with the condition.

1.9. The committee noted that MCAHS is a serious multi-system genetic condition caused by a defect in glycosylphosphatidylinositol (GPI) biosynthesis. To date, mutations in three different genes have been reported to cause MCAHS. MCAHS1 is caused by mutation in the gene PIGN (at chromosome location 18q21.33); MCAHS2 is caused by a mutation in the PIGA gene (at chromosome location Xp22.2) and MCAHS3 is caused by mutation in the PIGT gene (at chromosome location 20q13.12). MCAHS1 is already licensed for PGD with the HFEA. All three genetic forms of MCAHS are characterised by early onset seizures that may not respond to anticonvulsant therapy, profound intellectual disability, severe lack of muscle development and, in a majority of reported cases, death in early childhood. MCAHS is also associated with congenital abnormalities affecting the cardiac, urinary, gastrointestinal and central nervous systems. The effects of this condition can become apparent in utero or in infancy.

1.10. The most common symptoms of MCAHS include hypotonia, seizures, and severe motor and intellectual delay. While there are some subtle differences reported between the three different genetic types, the overall pattern of multi-system abnormalities is very similar. Variable and significant anomalies are observed in multiple organs, including cardiovascular, respiratory, genitourinary, skeletal, central-nervous and gastrointestinal systems. Patients may have impaired vision and/or deafness. There is some variation in the pattern of associated congenital abnormality but learning disability and seizures are a consistent finding. As MCAHS2 is X-linked it mainly affects males, whereas MCAHS3 is autosomal recessive. Penetrance of MCAHS3 is 100% in children inheriting two altered copies of the PIGT gene and, in MCAHS2, is 100% in males inheriting a mutated PIGA gene.

1.11. The committee noted that some of the symptoms can be managed, but the condition is incurable, and most reported patients have died by the age of three. Seizures can be managed, but this does not modify the underlying disease or the progression of the disease. Those who live longer are severely affected with a significant impact on quality of life and still have a shortened life expectancy.

1.12. The committee noted that MCAHS1, OMIM #614080 has already been approved as a condition for which PGD can be undertaken, acknowledging the minutes included in the papers. The peer review states that "the phenotypic differences between Type 1 and Types 2 and 3 are insignificant".

1.13. The committee noted the inspectorate's request to consider whether Multiple Congenital Anomalies Hypotonia-Seizures-Syndrome (MCAHS) including Multiple Congenital Anomalies Hypotonia-Seizures-Syndrome Type 3 (MCAHS3), OMIM #615398 and Multiple Congenital Anomalies Hypotonia-Seizures-Syndrome Type 2 (MCAHS2), OMIM #300868 should be approved for inclusion on the PGD List. The committee agreed to consider the application on this basis.

2. Decision

2.1. The committee considered that, in the worst case scenario, Multiple Congenital Anomalies Hypotonia-Seizures-Syndrome (MCAHS) including Multiple Congenital Anomalies Hypotonia-Seizures-Syndrome Type 3 (MCAHS3), OMIM #615398 and Multiple Congenital Anomalies Hypotonia-Seizures-Syndrome Type 2 (MCAHS2), OMIM #300868 are serious conditions due to the early onset and death in infancy, with many patients dying before the age of three. The quality of life for affected individuals and their families is severely impacted.

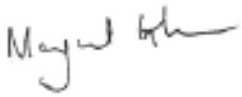
2.2. The committee had regard to its explanatory note and confirmed that, on the basis of the information presented, it was satisfied that there is a particular risk that an embryo may have the abnormality in question and that there is a significant risk, given the condition's worst symptoms, that a 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 conditions Multiple Congenital Anomalies Hypotonia-Seizures-Syndrome (MCAHS) including Multiple Congenital Anomalies Hypotonia-Seizures-Syndrome Type 3 (MCAHS3), OMIM #615398 and Multiple Congenital Anomalies Hypotonia-Seizures-Syndrome Type 2 (MCAHS2), OMIM #300868 meet the criteria for testing under paragraph 1ZA(1)(b) and (2) of Schedule 2 of the Act and agreed to authorise testing.

2.3. The committee agreed to authorise testing for Multiple Congenital Anomalies Hypotonia-Seizures-Syndrome (MCAHS) including Multiple Congenital Anomalies Hypotonia-Seizures-Syndrome Type 3 (MCAHS3), OMIM #615398 and Multiple Congenital Anomalies Hypotonia-Seizures-Syndrome Type 2 (MCAHS2), OMIM #300868.

3. Chairs signature

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

Signature



Name

Margaret Gilmore

Date

3 October 2018