Statutory Approvals Committee – minutes

Centre 0035 (Oxford Fertility)

Pre-implantation Genetic Diagnosis (PGD) application for

Aarskog-Scott Syndrome caused by mutations in FGD1, OMIM #395400

Thursday, 30 November 2017

HFEA, 10 Spring Gardens, London, SW1A 2BU

Committee members	Margaret Gilmore (Chair) Anne Lampe Anthony Rutherford Bobbie Farsides	
Members of the Executive	Bernice Ash Dee Knoyle Francs Metcalf-Head	Committee Secretary Committee Secretary (Observing) Inspections and Logistics Officer (Observing)
External adviser	Dr Alison Male	
Legal Adviser	Philip Grey	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
- Minutes of previous considerations of the condition on 29 May 2014 and 28 August 2014

1. Consideration of application

1.1. The committee welcomed the advice of its Specialist Adviser, Dr Alison Male, who noted that the description of the condition in the application was not restricted to the information published about cases with a confirmed mutation in the FGD1 gene, but also included features from cases published with a clinical diagnosis of Aarskog but no molecular diagnosis. Dr Male felt that the information in the peer review was more consistent with information published about cases with a confirmed FGD1 mutation. Dr Male also noted that the experiences reported in the survey conducted by The Aarskog Foundation were more severe than would be inferred from the peer review but there was no indication within the survey as to the molecular status of the patients / families who responded.

1.2. The committee noted that the description in the application for Aarskog-Scott syndrome, OMIM #305400 is not fully consistent with the peer review.

1.3. The committee noted that the Genetic Alliance opinion provided a patient perspective and supported the application. When contacted by the Genetic Alliance, The Aarskog Foundation had requested that the condition is called Aarskog Syndrome, as this is the name commonly used in the UK. The committee agreed to proceed with the application on this basis.

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 the condition is X-linked recessive which means, if the mother is a carrier, 50% of male embryos will be affected and 50% of female embryos will be carriers (may be mildly affected or not affected). In total 25% of the embryos will be affected and 25% will be carriers.

1.8. The committee noted that Aarskog syndrome, also known as facio-genital dysplasia, is an X-linked disorder characterised by short stature, hypertelorism (wide-spaced eyes), shawl scrotum and undescended testes, and brachydactyly (short fingers), although there is wide phenotypic variability and other features, such as joint hyperextensibility, short nose, widow's peak, and inguinal hernia, may also occur. Most patients do not have mental retardation, but some may have behavioural problems. Carrier females may present with subtle features, such as widow's peak or short stature.

1.9. Short stature and maybe somewhat unusual facial appearance are the most noticeable feature of this condition and affected individuals from different families may look strikingly similar. It is not progressive and the facial feature may become less obvious with age. Surgery may be required to treat undescended testes.

1.10. The committee noted that there is limited literature on this condition. The committee noted a 2010 paper that studied 60 patients presenting with symptoms of Aarskog-Scott syndrome. This paper established that only 11, out of the 60 patients, were confirmed to have a mutation in the FGD1 gene.

1.11. The committee noted that an application was made in 2014 for Aarskog-Scott syndrome, OMIM #305400, to be added to the list of conditions for which PGD can be applied. This application was refused as the committee agreed it did not have enough evidence or information to make a decision.

1.12. The committee considered the literature, focusing on patients with a mutation in the the specific gene, FGD1, and noting the malformations present. Consideration was given as to whether these abnormalities meet the level of seriousness required to approve this condition for inclusion on the PGD List.

1.13. The Legal Adviser guided the committee to the decision tree, asking them to consider the significance of the abnormalities associated with this condition and whether these can be explicitly linked to mutations in the specific gene, FGD1, linked to Aarskog-syndrome.

1.14. The committee noted the inspectorate's request to consider whether Aarskog-syndrome caused by mutations in FGD1, OMIM #305400, 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 had regard to its explanatory note. However, on the basis of the information presented, the committee was not satisfied that, even in extreme cases, the condition when caused by a mutation in the FGD1 gene met the significance and seriousness criteria required.

2.2. The committee reviewed the evidence provided in this application, including information from the Genetic Alliance, incorporating a survey conducted by The Aarskog Foundation, and the peer review, noting the discrepancies presented.

2.3. The committee had considered the application afresh from the decisions made at meetings held on 29 May 2014 and 28 August 2014.

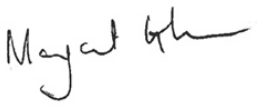
2.4. In taking into account the condition at its worst, and without further evidence other than that submitted in the papers and by the Specialist Adviser, the committee decided that it was not satisfied that the condition Aarskog syndrome, OMIM #305400 meets the criteria for testing under paragraph 1ZA(2)(b) and (2) of Schedule 2 of the Act.

2.5. The committee noted that the centre could resubmit the application, at some further time, should additional information and research become available.

3. Chair's signature

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

Signature



Name

Margaret Gilmore

Date

19 December 2017