Statutory Approvals Committee – minutes

Centre 0201 (Edinburgh Assisted Conception Unit) Pre-implantation Genetic Diagnosis (PGD) application for Pituitary Adenoma Type 1, OMIM #102200, Acroleukopathy, Symmetric, OMIM #102000, Pituitary Adenoma Type 2, OMIM #300943, Pituitary Adenoma Type 5, OMIM #617540

Thursday, 31 January 2019

Church House, Dean's Yard, Westminster, London. SW1P 3NZ

Committee members	Margaret Gilmore (Chair) Bobbie Farsides (Deputy Chair) Emma Cave Ruth Wilde Rachel Cutting	
Members of the Executive	Bernice Ash Dee Knoyle Paula Robinson Sandrine Oakes Nicola Lawrence	Committee Secretary Committee Secretary (Observer) Head of Planning and Governance (Observer) Inspector (Observer for Induction) Inspector (Observer for Induction)
Specialist Adviser	Dr Jenny Carmichael	
Legal Adviser	Tom Rider	Field Fisher 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:

- 9th 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
- Email from Person Responsible regarding the condition names applied for
- Redacted Peer Review
- Genetic Alliance UK statement

1. Consideration of application

1.1. The committee welcomed the advice of its Specialist Adviser, Dr Jenny Carmichael, who confirmed that the condition was as described in the papers.

1.2. The committee noted that the description in the application for AIP-related Familial Isolated Pituitary Adenoma OMIM #102200, OMIM #300943 and OMIM #617540 is consistent with the peer review. AIP is the aryl hydrocarbon receptor interacting protein (OMIM *605555).

1.3. The committee noted that the Executive verified the condition names, originally applied for the application, on the OMIM website, finding they relate to Pituitary Adenoma Type 1, OMIM #102200, Acroleukopathy, Symmetric, OMIM #102000; Pituitary Adenoma Type 2, OMIM #300943 and Pituitary Adenoma Type 5, OMIM #617540. At this stage, the applicant stated they wanted to reduce the application to Pituitary Adenoma Type 1, OMIM #102200, and Acroleukopathy, Symmetric, OMIM #102000; the email, included in the papers, was acknowledged.

1.4. The committee noted that Pituitary Adenoma Type 2, OMIM #300943, and Pituitary Adenoma Type 5, OMIM #617540, are comparable and related subtypes to the condition applied for by the centre. The Executive reflected these should be considered by the committee, subsequent to their consideration of Pituitary Adenoma Type 1, OMIM #102200.

1.5. The committee noted that the Executive conducted further research on Acroleukopathy, Symmetric, OMIM #102000. The AIP gene entry, OMIM *605555, lists OMIM #102000 as ‘Pituitary adenoma predisposition’, an AIP mutation-related phenotype. In contrast, the specific entry for OMIM #102000 relates to Acroleukopathy, Symmetric, which causes de-pigmentation around the hands and feet, and not relevant to the other conditions applied for by the centre. As PGD cannot be granted for predisposing factors, since they are not directly causative of a condition, and given the confusion of naming, the Executive considered that an application for this OMIM number could not progress. The committee acknowledged the email from the PR, confirming the application is only for Pituitary Adenoma Type 1, OMIM #102200.

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

1.7. 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.

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

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 Pituitary Adenoma Type 1 and Pituitary Adenoma Type 5 are inherited in an autosomal dominant pattern which means there is a 50% chance of an embryo inheriting the condition in each pregnancy, if either parent has a relevant mutation.

1.11. The committee noted that Pituitary Adenoma Type 2 is inherited in an X-linked dominant pattern, which means there is 50% chance of having an affected child in each pregnancy if either parent has a relevant mutation.

1.12. The committee noted that Pituitary Adenoma Type 1, Pituitary Adenoma Type 2 and Pituitary Adenoma Type 5 are all genetic conditions which can increase the likelihood of developing a pituitary gland tumour, known as an adenoma (non-malignant), which is not associated with tumours of any other glands or associated with any other abnormalities other than the complications arising from the tumour itself. These pituitary adenomas tend to occur at a younger age and are more difficult to control, being more resistant to medical treatment and more likely to re-occur, than adenomas which are not related to genetic mutations.

1.13. Pituitary Adenoma Type 1 is caused by a mutation in the AIP gene, Pituitary Adenoma Type 2 by a mutation in the GPR101 gene and Pituitary Adenoma Type 5 by a mutation in the CDH23 gene. In Pituitary Adenoma Type 2 growth acceleration can manifest as early as two months of age with all patients showing symptoms before the age of 4. For Pituitary Adenoma Type 1 and Pituitary Adenoma Type 5 the age of onset of these tumours varies, the youngest known case being at 6 years and the oldest at 78 years. The median age of diagnosis is 23 years.

1.14. The pituitary gland produces 8 different hormones that control growth, fertility thyroid function and regulate the stress hormone cortisol. Pituitary adenomas can lead to excessive secretion of these pituitary hormones which results in a large range of symptoms. Increased growth hormone secretion causes acromegaly, leading to exceptionally tall stature, enlarged hands and feet, coarse facial appearance, headaches and hypertension, amongst other symptoms. Increased prolactin secretion causes prolactinaemia leading to infertility, irregular periods and galactorrhoea (milky discharge from the nipple not related to breastfeeding). Increased thyroid stimulating hormone (TSH) secretion causes hyperthyroidism leading to anxiety, mood swings, difficulty sleeping and weight loss. Increased adrenocorticotrophic hormone (ACTH) secretion causes Cushing disease leading to centralised obesity, moon facies, diabetes, hypertension and an increased risk of cerebrovascular and cardiovascular disease.

1.15. Adenomas can also reduce secretion of pituitary hormones either due to the tumour or following surgical removal of the pituitary gland. This can cause subfertility, hypothyroidism, hypoadrenalism, low levels of growth hormone and panhypopituitarism. Larger pituitary tumours can cause Pituitary Apoplexy (insufficient blood supply to the pituitary gland) which results in sudden-onset severe headaches, visual disturbances, cranial nerve palsies, low blood sugar levels, and low blood pressure shock. They can also cause local pressure effects by invading neighbouring structures of the brain including the optic chiasm and cavernous sinus, this can lead to visual disturbance. Patients with Pituitary Adenoma Type 2, both male and female, are likely to develop X-linked acrogigantism which leads to growth acceleration enlarged hands and feet, coarse facial features and increased appetite.

1.16. The committee noted that the penetrance of Pituitary Adenoma Type 1 and Pituitary Adenoma Type 5 is thought to be around 15-30%. The penetrance of Pituitary Adenoma Type 2 has so far been shown to be 100% including even ‘carrier’ females and hemizygous males.

1.17. The Peer Reviewer noted that Chromosome Xq26.3 Duplication Syndrome, OMIM #300942, should also be included within this application as it phenotypically similar to Pituitary Adenoma Type 2, OMIM #300943, and has a similar inheritance pattern. Chromosome Xq26.3 Duplication Syndrome, OMIM #300942, is caused by a duplication in the GPR101 gene and leads to “excessive growth, usually beginning in the first year of life”.

1.18. The Specialist Advisor informed the committee that, although Chromosome Xq26.3 Duplication Syndrome, OMIM #300942, has some features associated with Pituitary Adenoma Types 1, 2 and 5, it is not specifically a genetic condition primarily associated with pituitary adenomas, making reference to a study of 248 patients with acromegaly and pituitary adenomas, whereby only 3 out of 248 individuals were identified with a GPR101 mutation in the germline. The Specialist Advisor recommended that Chromosome Xq26.3 Duplication Syndrome, OMIM #300942 should not be considered for approval for inclusion on the PGD List as a separate item. The committee accepted this advice.

1.19. The committee noted the inspectorate's request to consider whether Pituitary Adenoma Type 1, OMIM #102200, should be approved for inclusion on the PGD List. The inspectorate thereafter requested the committee consider whether Pituitary Adenoma Type 2, OMIM #300943 and Pituitary Adenoma Type 5, OMIM #617540 should also be added to the PGD List. The committee was further asked to consider if Chromosome Xq26.3 Duplication Syndrome, OMIM #300942 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, Pituitary Adenoma Type 1, OMIM #102200, Pituitary Adenoma Type 2, OMIM #300943 and Pituitary Adenoma Type 5, OMIM #617540, are serious and unpredictable conditions, requiring lifelong screening, treatment and surgeries, and can be fatal. The conditions are multi-system disorders, affecting the structures of the brain. The conditions severely impact on the individual's quality of life and the family.

2.2. The committee proceeded to consider the inspectorate's request to consider whether Chromosome Xq26.3 Duplication Syndrome, OMIM #300942, should be added to the list of conditions for which PGD can be applied. Considering the advice of the Specialist Advisor, noting this is a genetic condition not specifically and exclusively linked to pituitary adenomas, the committee agreed not to authorise testing for Chromosome Xq26.3 Duplication Syndrome, OMIM #300942.

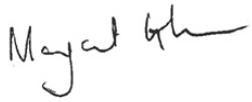
2.3. The committee had regard to its explanatory note and confirmed that, on the basis of the information presented, it was satisfied that there is a particular risk that an embryo may have the abnormality in question and that there is a significant risk, given the conditions' worst symptoms, that a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

- Pituitary Adenoma Type 1, OMIM #102200
- Pituitary Adenoma Type 2, OMIM #300943
- Pituitary Adenoma Type 5, OMIM #617540

3. Chairs signature

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

Signature



Name

Margaret Gilmore

Date

25 February 2019