Statutory Approvals Committee - minutes

Centre 0341 (The Fertility & Gynaecology Academy)

Preimplantation Genetic Diagnosis (PGD) application for Human Leukocyte Antigen C (HLAC2)

Date:	25 February 2021
Venue:	Microsoft Teams Meeting
Committee Members:	Margaret Gilmore (Chair) Emma Cave Anne Lampe Ruth Wilde
Specialist Adviser:	Alan Fryer
Legal Adviser:	Sarah Ellson - FieldFisher LLP
Members of the Executive:	Moya Berry - Committee officer Catherine Burwood - Licensing Manager
Observers:	Sarah Steadman - Inspector (Induction) Karen Campbell - Inspector (Induction)
Apologies:	No apologies were received for the meeting
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:

- HFEA Code of Practice 9th edition
- Standard Licencing and Approvals Pack

The following papers were considered by the committee:

- Executive Summary
- PGD Application form
- Redacted Peer review

1. Consideration of application

1.1. The committee welcomed the advice of its specialist adviser, Alan Fryer.

1.2. The committee noted that a description of the Human Leukocyte Antigen C (HLA-C2) genotype was provided in the application and peer review.

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

1.4. The committee noted that a Genetic Alliance (UK) statement had not been provided for this application.

1.5. The committee noted that this application describes the centre's wish to test embryos for the HLA-C2 genotype, to avoid a risk of miscarriage the centre considers to be present because the mother exhibits a killer cell immunoglobulin-like receptor (KIR) 'AA' genotype. No comparable condition or phenotype is listed on the OMIM website. The committee noted that no OMIM number is provided by the centre.

1.6. The committee noted that the centre first applied for authorisation to undertake this testing through the 'HLA-tissue typing' pathway. However, the executive considered that the centre's proposed testing fell outside the scope of the HLA tissue typing application pathway and was potentially relevant to being considered within the PGD authorisation pathway.

1.7. The committee received advice from its legal adviser who confirmed the executive's view that the centre's original request for HLA-Tissue Typing testing was incorrect. Testing under Schedule 2 paragraph 1ZA(1) (d) of the HFE Act 1990 allows for HLA tissue typing embryo testing but only to establish whether the tissue of any resulting child would be compatible with an existing sibling who suffers from a serious medical condition which could be treated by umbilical cord blood stem cells, bone marrow or other tissue of any resulting child. This application was considered to be more suited to the PGD authorisation pathway and the PGD decision tree was the most relevant for the committee in considering this application.

1.8. The legal adviser asked the committee to note the precise wording from Schedule 2 and in particular paragraphs 1ZA(1)(a) and (1)(b): 'Testing of an embryo is permitted for the purpose of (a) establishing whether the embryo has a gene, chromosome or mitochondrion abnormality that may affect its capacity to result in a live birth, or (b) in a case 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.'

1.9. Testing under 1(b) can only be authorised if the committee is satisfied (in relation to the abnormality) there is a particular risk (mode of inheritance informs this), and that there is a significant risk 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. In the committee's decision tree and the explanatory notes this is framed as considering risks to the resulting child and an affected person. The legal adviser commented that the committee may consider that 1(b) is a poor fit in this case, since the application does not concern the physical or mental disability, illness, or medical condition of a resulting child. Rather, it concerns, whether the embryo exhibits the HLA-C2 genotype in mothers with the KIR 'AA' genotype', which the application suggests might compromise placentation or result in implantation failure, miscarriage, intrauterine growth restriction and preeclampsia, leading to maternal and fetal/neonatal morbidity and mortality.

1.10. The legal adviser advised that the more appropriate proposed purpose for testing would appear to be 1ZA(1)(a) to establish "whether the embryo has a gene, chromosome or mitochondrion abnormality that may affect its capacity to result in a live birth".

1.11. The committee noted the UK population frequency of maternal KIR AA and Human Leukocyte Antigen C:HLA-C2 genotype is 30%, but when this is combined with the paternal HLA-C2, the application suggests that there is a 40% chance of having a KIR-AA/HLA-C2 combination in the embryo leading to implantation failure and miscarriage.

1.12. The committee received advice from its specialist adviser who explained that the application does not refer to a genetic/chromosomal/mitochondrial abnormality but rather the identification of risk factors for a poor pregnancy outcome. The specialist adviser explained that the data is not at a stage where a clear picture on the association between KIR and HLA variants and recurrent miscarriage can be provided, and that recent review articles indicate that the data suggesting that MHC-KIR genes or molecules may play a role in recurrent miscarriage are preliminary and varying. The specialist adviser stated that further clinical research is required to prove the link and, if proven, provide robust data on the level of the risk of associated pregnancy loss before such testing was clinically applicable.

1.13. The committee noted the executive's request to consider Human Leukocyte Antigen C (HLA-C2), for inclusion on the list of conditions approved for PGD for the proposed purpose of testing the embryos as set out in paragraph 1ZA(1)(b) of schedule 2 of the Act. The committee agreed that it could not consider the application on this basis for the reasons above. Rather, the committee decided to consider the application under 1ZA(1)(a) to establish "whether the embryo has a gene, chromosome or mitochondrion abnormality that may affect its capacity to result in a live birth".

2. Decision

2.1. The committee accepted the advice of its legal adviser and focused first on the purpose of testing under 1ZA(1)(a). It noted that the testing proposed was to establish whether an embryo exhibits the HLA-C2 genotype in mothers with the KIR 'AA' genotype.

2.2. The committee's view was that this application was not requesting testing for a gene, chromosome or mitochondrion abnormality. HLA-C2 genotype is not an "abnormality" in the ordinary meaning of the word. Indeed, the application states that in the UK population the frequency of the combination of maternal KIR AA and HLA-C2 genotype is 30%. The committee therefore concluded that, in the absence of testing for an abnormality, it did not have the necessary powers under the legislation to authorise testing for this genotype.

2.3. The committee went on to consider whether, even if it did have such a power, it could be satisfied that the characteristics for which the embryo would be tested might indeed affect capacity to result in a live birth. Based on the advice of its specialist adviser, the committee took into consideration that the evidence of the association between KIR and HLA variants and the risk of recurrent miscarriage is preliminary. They agreed that there was currently not enough sound data to be satisfied that testing to identify specific KIR-HLA-C2 combinations could reduce the risk of implantation failure and/or miscarriage, pre-eclampsia or fetal restriction that would affect the embryos capacity to result in a live birth. The committee noted that the peer review and specialist adviser quoted from a 2017 review (Immunogenetics (2017) 69; 557-565) which stated that "*None of the studies on recurrent miscarriage appears conclusive*" and that "*Despite compelling evidence we are still far from clinical applications*".

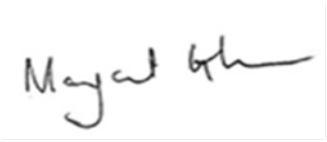
2.4. In coming to its conclusion, the committee acknowledged the sadness and emotional distress associated with recurrent miscarriage, and the psychological impact it may have on those affected.

2.5. Therefore, after very careful consideration and deliberation, the committee decided that the application is **not** authorised.

3. Chair's signature

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

Signature



Name

Margaret Gilmore

Date

17 March 2021