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ORIGINAL ARTICLE

Genetic screening in gamete donation: Recommendations from SEF, ASESA, AEBM-ML, ASEBIR and AEGH

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Abstract Recommendations are made for the genetic screening of gamete donors. These recommendations are the result of the consensus reached by a work group consisting of representatives from the Spanish Fertility Society, the Spanish Association of Andrology, the Spanish Association of Medical Biopathology and Laboratory Medicine, the Association for the Study of

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◊ SEF: Spanish Fertility Society, ASESA: Spanish Association of Andrology, AEBM-ML: Spanish Association of Medical Biopathology and Laboratory Medicine, ASEBIR: Association for the Study of Reproductive Biology, AEGH: Spanish Association of Human Genetics.

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Reproductive Biology and the Spanish Association of Human Genetics and were subsequently reviewed and approved by the executive boards of each of these associations. This document describes 2 types of genetic screening: a basic mandatory screening of all donors and an extended genetic screening for donor-recipient genetic matching. The importance of pre- and post-screening genetic counselling, the management of the occurrence of adverse reactions of a genetic nature and the use of informed consent from donors who accept the management of their DNA samples stored in the centre's bank are emphasized. The role of informed consent to find out patients' opinions on what type of screening they want to be carried out, their desire to know the results of the screening and aptitude for future genetic data is also highlighted.

PALABRAS CLAVE
Donación de gametos;
Cribado genético;
Enfermedades recesivas;
Emparejamiento genético

Cribado genético en donación de gametos: recomendaciones SEF, ASESA, AEBM-ML, ASEBIR y AEGH

Resumen Se presentan recomendaciones para la realización del cribado genético de donantes de gametos. Estas son fruto del consenso alcanzado por un grupo de trabajo compuesto por representantes de la Sociedad Española de Fertilidad, Asociación Española de Andrología, Asociación Española de Biopatología Médica-Medicina de Laboratorio, Asociación para el Estudio de la Biología de la Reproducción y Asociación Española de Genética Humana. Posteriormente fue revisado y aprobado por cada una de las juntas directivas de estas sociedades. El documento describe 2 tipos de cribado genético, uno básico obligatorio a todos los donantes y un cribado genético ampliado para «matching» o emparejamiento genético donante-receptor. Se destaca la importancia del asesoramiento genético pre y poscribado, protocolo ante la aparición de reacciones adversas de carácter genético, el uso de los consentimientos informados de donantes aceptando la gestión de muestras de su ADN almacenado en el banco del centro. También se resalta el papel del consentimiento informado para conocer la opinión de los pacientes sobre qué tipo de cribado quiere que se realice, su deseo de conocer los resultados del cribado y aptitud ante futuros hallazgos de base genética.

Introduction

It is estimated that all human beings are carriers of pathogenic variants in one or more genes associated with recessive diseases or linked to the X chromosome (Fujikura, 2016). Individually, many of these diseases occur very infrequently in the population, so their diagnosis and possible treatment are extremely complex. Therefore, they are not very prevalent diseases and are known colloquially as 'rare diseases'. Diseases which affect less than 1 in 2000 inhabitants are considered rare diseases (FEDER: https://enfermedades-raras.org/index.php/enfermedades-raras). Together they affect around 30 million people in Europe and represent a major health problem.

It is estimated that 2 in 100 asymptomatic couples could have a genetic risk of transmitting one of these diseases to their offspring (Ropers, 2012). The use of donor gametes for reproductive purposes carries a similar natural risk. This risk can be decreased if the individuals who provide the gametes carry out genetic carrier screening with the aim of finding out the carrier status of each individual (donor and recipient) for hundreds of recessive genetic diseases or genetic diseases linked to the X chromosome.

In the context of assisted reproduction techniques (ART) which require the use of donor gametes, once the pathogenic variants of a gamete recipient are known, they will then be matched with a donor who is not a carrier of pathogenic variants in the same gene(s). This procedure is called genetic matching. In the context of reproductive genetic counselling, it would be advisable to inform healthy couples who attend Reproduction centres nowadays about the existence of expanded genetic carrier screening studies, so they could evaluate genetic risk and choose the option they consider to be most appropriate with the aim of avoiding a child being born with one of these studied genetic diseases.

At present, there are different expanded genetic carrier screening studies on the market. Each includes a different number of genes and diseases of varying severity in their panels, and in addition uses different technology (genotyping and/or sequencing) for the detection of pathogenic variants.

Aims

The aims of this document are to establish some basic recommendations regarding genetic carrier screening studies for donor gametes: (a) which diseases to include, (b) which results people have to be informed about and how they should be notified, (c) when a donor should be rejected or accepted, (d) how to manage the information about an affected newborn after a donation process and (e) how to manage factors such as anonymity for donors and DNA banks.

Material and method

In July 2017, a work group made up of 12 representatives from the Spanish Fertility Society, the Spanish Association of Andrology, the Spanish Association of Medical Biopathology and Laboratory Medicine, the Spanish Association for the Study of Reproductive Biology and the Spanish Association of Human Genetics was set up. After several face-to-face and virtual meetings, the resulting document was later revised and approved by the executive boards of each of these societies in July 2019. The final document can be consulted at https://www.sefertilidad.net/docs/noticias/cribadoGenetico.pdf

Results and discussion

Below, the 18 recommendations summarized in the aforementioned document are set out:

- The final aim of the expanded genetic carrier screening studies on gamete donors and recipients is to reduce the risk of having offspring who are affected by the serious hereditary diseases studied in the recipient.
- Serious hereditary diseases are considered to be those genetic diseases which significantly reduce the quality of life with a physical or intellectual deficiency, require lifelong surgical or medical treatment or reduce life expectancy due to emerging in the first few decades of life.
- Patients who turn to assisted reproduction treatments using donated gametes should be informed about the natural risk of having offspring affected by a serious hereditary disease.
- The natural risk of transmitting a serious hereditary disease stems from the fact that all human beings are carriers of variants in our DNA sequence. Some of these variants may be pathogenic and even if they do not affect the individual carrier, they can give rise to serious hereditary diseases in offspring due to being autosomal recessive inheritance diseases, or diseases linked to the X chromosome.
- It is estimated that the risk that both members of a couple are carriers of a pathogenic variant of the same gene is 2%. Therefore, patients should be informed about possible existing strategies to reduce the risk of having offspring affected by a serious hereditary recessive disease or one linked to chromosome X, which, in the event of not taking any preventative measures, is estimated at around 0.5%. It is important to emphasize that this risk is no higher when using donor gametes.
- As a starting point, and with the aim of reducing this risk, all gamete banks should carry out basic genetic screening on their donors. For their prevalence, penetrance and severity, this basic genetic screening should include the analysis of pathogenic variants related to cystic fibrosis (CFTR), spinal muscular atrophy (SMN1), non-syndromic sensorineural deafness (GJB2) and the most prevalent hemoglobinopathies (HBA1/HBA2, HBB; alpha and beta thalassemia, sickle-cell anaemia). In addition, in oocyte donors, the molecular study of the FMR1 gene related to fragile X Syndrome.
- Another recommended strategy which all patients should be informed about is based on carrying out expanded genetic carrier screening on all individuals who provide gametes for assisted reproduction techniques. If donor gametes are used in these techniques, donors who do not share pathogenic variants in the same gene as the recipient will be selected. This is called genetic matching.
- In any case, patients should be informed that none of these strategies guarantee the birth of a child without a serious hereditary disease, due to the limitations of any laboratory test and because there are thousands of pathogenic variants whose frequencies of carriers, penetrance, expressivity and severity do not justify them being included in a screening panel. In addition, there is also the possibility of the appearance of genetic diseases in offspring due to de novo mutations.
- Donors who have pathogenic variants in the diseases included in the basic genetic screening can only be used when the existence of pathogenic variants in the recipient is ruled out (Genetic Matching) and in the case of the molecular study of Fragile X Syndrome, they will be rejected in light of the risk of transmitting this syndrome. Genetic information about donors obtained through basic screening or expanded genetic carrier screening will be disclosed to donors since it is their personal information, unless they have opted not to receive this information before the study was carried out. This information could be given by professionals from the reproductive centre, gamete bank or the genetic centre where the study has been carried out. In the same way, donors will decide whether they want to be contacted and informed in the event that a serious genetic risk to them or their offspring is discovered in the future.
- Each gamete bank can decide which diseases to include in these expanded genetic carrier screening studies, taking into account that these panels should be limited to serious diseases with defined phenotypes and variants of high penetrance, with a high frequency of carriers and a causal relationship between the pathogenic variant and the phenotype, avoiding identifying variants of unknown biological significance. On the contrary, low risk and/or false positive donors could be excluded from reproduction programmes, and this could result in possible harm to the donor candidate and also for the selection of the most suitable donor for certain patients. In any case, oocyte donors with pathogenic variants in genes linked to the X chromosome will be rejected.
- Taking into account that any individual could be a carrier of one or more pathogenic variants, that the presence

of these may not affect their health or their offspring's health and that some of these variants are extremely infrequent, a donor who is a carrier of recessive diseases of low prevalence (lower than 1/60) can be used without knowing the genetic status of the recipient. Patients should be informed about this in the informed consent.

- Recipient patients should not be informed of the donor's pathogenic variants for several reasons: firstly, because this information does not belong to these patients but rather to the donor and its revelation could put their anonymity at risk. Secondly, because it is unnecessary information for patients, and knowing it could give rise to them rejecting a donor, influencing donor selection. The allocation of a donor is by law carried out by the centre's medical team.
- If a gamete donation results in offspring affected by a hereditary disease, each case should be evaluated individually by a multidisciplinary team who will decide whether or not to withdraw the donor.
- It has to be taken into account that gametes from one donor could be used for several patients, which means the necessity of having a control on birth children, in order to avoid the risk of consanguinity, and therefore, a greater incidence of genetic abnormalities in the offspring of these couples who are unknowingly consanguineous. Based on the effectiveness of treatment and the social and demographic reality of our country, the maximum limit of live births in Spain per gamete donor estimated by the SEF (2018) should range from 20 family units with newborns or 25 newborns. With these figures, the probability that both members of a couple have the same donor as their biological parent is lower than the probability that this occurs naturally. However, current Spanish legislation still limits the number of birth children per donor in Spain to six.
- It is recommended that centres or genetic testing laboratories organize DNA banks of donors since (as has already been mentioned) it is not possible to analyze all the pathogenic variants of a donor, and in the event of offspring appearing with diseases suspected to be of a genetic basis, having this material might be essential for an exact affiliation of its aetiology. This assumption, together with the existence of late-onset genetic diseases and the impossibility on many occasions of locating the gamete donors, makes it increasingly necessary to have banks of DNA samples for later genetic studies. Donors should accept these conditions through specific informed consent for the DNA bank. They should also indicate whether they want to know about the new genetic information obtained, and authorize that their DNA sample may be sent to a different centre from that previously authorized, in order to carry out studies with the same original purpose.
- The handling of genetic information, both for donors and the couples who benefit from donation programmes, should be carried out in the context of suitable genetic counselling before and after the genetic studies which are chosen for each case. Regarding the possibility of contacting patients and donors about new findings, it is considered that the criterion for deciding whether or not to do so should be focused on specific situations with significant clinical consequences for the recipient, their offspring or the donors themselves (thinking about their reproductive futures), in the medical team's opinion. That is to say, it would be appropriate to contact them in cases where from a medical point of view the pathology is considered to be relevant to the health of the person affected and it is reasonably possible to take some preventive or curative measure. It is recommended that patients and donors are advised to delegate to the medical team the decision about when they want to be contacted.
- We can conclude that nowadays it is not possible to completely avoid the transmission of serious hereditary diseases to offspring following the use of donor gametes. In spite of this, due to basic genetic screening, genetic matching and the control on the number of birth children per donor, the risk can be significantly reduced.
- Public authorities have the duty to stimulate social debate on these issues and try to reach a consensus which guarantees accessibility to health services which demonstrate a clear improvement in health. These debates between professionals and other social agents should consider the genetic risks in human reproduction and the limits in preventing them in ART. It is essential that patients and other social agents (especially lawyers and judges) are informed that births of children affected by recessive genetic diseases following the use of donated gametes will continue to happen despite informing patients about the existence of expanded genetic carrier screening studies. Every time this happens after using donated gametes, it cannot be attributed to the use of these gametes, but as inherent to the biological condition of humans. On the contrary, the existence of ART may be threatened, since centres and their professionals will not be able to withstand the legal consequences of the births of children affected by recessive diseases following the use of donated gametes in informed patients.

Conflict of interest

The authors declare no conflict of interest.

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