Genetic matching between recipients and oocyte donors

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Summary

The aim of this paper is to describe the implementation of an extended carrier screening in our oocyte donation programme with the objective of reducing the risk of transmission of recessive genetic diseases. The panel used was qCarrier test, an NGS expanded carrier screening (ECS) that included 200 genes (68 with complete sequencing of the coding region and 132 targeting known mutations) associated with 277 autosomal recessive and 37 X-linked diseases.

The ECS was performed to most oocyte candidate donors and the male partner recipients, since November 2013. Donors who were carriers for X-linked conditions were excluded from the programme, while carriers for autosomal recessive conditions were not excluded, but the information was considered in the genetic-matching process. The definitive matching was done only when genetic results were available, taking into account that donor and recipient were not carrying mutations for the same gene/disease.

Genetic counselling at different stages of the process was considered essential in order to achieve the purposes of incorporating the test and giving appropriated information and counselling before and after genetic testing.

The implementation of the ECS in our gamete donation programme exceeded 80% and identified 56% of donors and recipients that were carriers for at least one of the genetic conditions included in the test. Approximately 2% of female donors was excluded from the donation programme due to a carrier state of X-linked conditions, and 3.5% of assigned donations with a high reproductive risk was identified. The use of an NGS carrier screening for both donors and recipients proved to be a very useful tool to reduce the risk of transmission of genetic conditions in children born from the oocyte donation programme.

KEY WORDS: genetic matching, autosomal recessive mutations, X-linked diseases, expanded carrier screening, next generation sequencing.

Introduction

Oocyte donation (OD) is an increasing option amongst infertile couples and according to the latest published report of the European Society of Human Reproduction and Embryology (ESHRE), it was used in 4.6% of assisted repro-
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production techniques (ART) cycles across Europe, and in 22% of ART cycles in Spain. Spain is the country that performs more than 15,000 OD cycles which represents 52% of the European OD cycles (1). This fact could be probably explained by the Spanish legal framework as well as the good quality of ART. According to the Spanish law on ART (Law 14/2006) (2), egg donation must be anonymous without seeking financial gain but a financial compensation to donors is allowed. This is in tune with the European Tissues and Cells Directive (EC/2004/23) (3) that postulates that donation programmes should be founded on the philosophy of voluntary and unpaid donation but without prejudice to the legislation of each country.

Concerning donor screening, the protocol established in Spain has to include phenotypical and psychological characteristics, clinical and analytical studies to show that, according to present scientific and technological knowledge at the time of the treatment, the donors do not suffer from any inherited genetic or infectious diseases that can be transmitted to the offspring. The European Commission Directive EC/2006/17 (4) as regards certain technical requirements, procurement and testing of human tissues and cells, postulates that donors must be selected on the basis of their age, health and medical history. This assessment must include relevant factors that may assist in identifying and screening out persons whose donation could present health risks to others, such as the possibility of transmitting diseases and health risks to themselves. Donors must be negative for HIV1, HIV2, HCV and Syphilis. HTLV-I antibody testing must be performed for donors living in or originating from high-incidence areas, or with sexual partners originating from those areas, or where the donor’s parents originate from those areas. In certain circumstances additional testing may be required depending on the donor’s history and the characteristics of the donated tissue or cells (e.g. RhD, malaria, CMV, T. cruzi). Regarding genetic tests, the norm postulates that genetic screening for autosomal recessive genes known to be prevalent, according to international scientific evidence in the donor’s ethnic background and an assessment of the risk of transmission of inherited conditions known to be present in the family, must be carried out after consent is obtained.

With regard to matching between donor and recipients, the Spanish law specifies that the donor can only be chosen by the medical team that performs the technique and in no case can the donor be chosen personally by the recipient. The medical team involved must guarantee the greatest possible phenotypical and immunological similarity of the available samples with the recipient. Until recently, professionals were usually aware of ethnicity, blood group and Rhesus factor, and personal characteristics like weight and height, skin, hair and eyes for the phenotypical and immunological matching. Traditionally, for genetic screening and matching, a karyotype and genetic screening only for diseases with high prevalence like cystic fibrosis were considered although not all centres performed them. Despite this genetic screening, several cases of children born from gamete donation affected with autosomal-recessive diseases have been reported (5, 6). As a consequence of it, the extension of carrier screening to a larger number of genetic conditions has be proposed.

During the last few years, genetics has experienced important technological advances. The emergence of technologies such as next-generation sequencing (NGS), allows the analysis of a large number of genes and the concurrent evaluation of hundreds of mutations (7). Since NGS technologies are capable of cost-efficient detection of a wider range of disease-causing mutations, some ART centres consider the implementation of an Expanded Carrier Screening (ECS) in OD programmes. The American College of Medical Genetics has established that these tests should include severe disorders associated with significant adverse outcomes that could cause a change in the reproductive context. However, genes that cause adult-onset diseases, complex disorders with variable expressivity, reduced penetrance and phenotypical features without clinical consequences should not be included (8).

In 2014 the ESHRE Task Force on Ethics and Law published a document regarding the ethical issues of genetic screening in OD (9). This document considers that proposals for ECS should be assessed in terms of its effectiveness and proportionality, taking the interests of all stakeholders (donors, recipients and their relatives) into account and highlighting the importance of informed consent and genetic counselling regarding the carrier status implications.

We report here the clinical implementation of an
ECS test based on targeted NGS of specific genes in our OD programme. We have developed the clinical pipeline and protocols for an efficient identification of carrier subjects, an adequate genetic counselling, and a suitable matching in order to decrease the number of affected newborns with genetic diseases.

**Dexeus’s experience**

The used Expanded Carrier Screening was the Carrier test, a panel developed in 2013 that included a total of 200 genes listed in the OMIM database (Online Mendelian Inheritance in Man, www.ncbi.nlm.nih.gov/omim) associated with 314 monogenic diseases: 277 autosomal-recessive and 37 X-linked (10). For gene selection, consideration was given to geographic prevalence (Mediterranean region), neonatal screening programmes and a selection of mutations associated with severe genetic diseases. The analysis was performed by complete sequencing of the coding region of the genes associated with the most prevalent diseases (68 genes) while a targeted-mutational analysis was performed for genes associated with rare diseases (132 genes). The new version of the Carrier test with a complete coverage of all the genes was not yet available at that moment.

The Reproductive Medicine Service of Women’s Health Dexeus started incorporating the ECS in the OD programme at the end of 2013. From November 2013 to June 2016, a total of 1,389 individuals were studied: 623 oocyte donors (44.8%) and 766 male partners of the recipients (55.2%) (11).

Genetic counselling was considered of crucial importance to get a good implementation of the test. For this reason, a Genetic Counsellor was incorporated in the reproductive team in order to provide the appropriate information and counselling by a well-trained professional in the field of genetics. Both donors and recipients had pre-test and post-test visits. In the pre-test session, the family history was obtained, explanations were given about the type of diseases, inheritance models, reproductive implications and finally the informed consent of the ECS was given. In the post-test session, results, reproductive risks and family recommendations if they were necessary, were given. Several important messages were given in the genetic counselling sessions. First of all that we are all carriers of recessive mutations and despite performing the ECS, genetic risks were not totally eliminated. Second, they were informed about the possible residual risk for some screened disorders. Moreover, although the chance of incidental findings is small, it was also explained that for some conditions the carrier status confers an increased risk for adult-onset diseases. All these issues must be extensively discussed in the pre-test counselling session and the informed consent must include the “right to know and right not to know”. Finally, it was explained that there are variants of unknown clinical significance (VUS) and their existence confers a certain degree of uncertainty.

The implementation of the ECS in the OD programme had a very good acceptance among our patients. Although the implementation rate was lower at the beginning, it exceeded 80% in the first semester of 2016. Among donor candidates, only three cases did not accept genetic screening after the pre-test session and approximately 5% of the oocyte donors were excluded from the programme because of an increased risk of diseases with a genetic component such as family history of hereditary breast or ovarian cancer among others.

Donors were pre-assigned to recipients based on phenotype but definitive matching was performed when genetic results of the ECS from donor and recipient partner were available. Both pathogenic variants and VUS were taken into account for the genetic match which is performed semi-automatically.

Results of the expanded carrier screening allowed the identification of approximately 2% carriers of X-linked conditions among donor candidates which and therefore they were excluded from the OD programme.

Less than one half of the individuals studied with the Carrier test were not carriers for pathogenic mutations in the genes included in the test, while more than 56% were carriers for at least one mutation (1-6 mutations). A carrier state for an autosomal recessive condition was not an exclusion criterion for the donor candidates. When donor and recipient had a mutation in the same gene, another donor was chosen and the first one came back to the pool of donors available for another matching. In those cases, “genetic-match” was performed ensuring that the donor and the recipient were not carriers for the same recessive condition.
The implementation of the ECS in the OD programme allowed the identification of 3.5% of pre-assigned donor-receptor matches with a high reproductive risk for an autosomal recessive genetic condition that required changing the selected donor for another without mutations in the same gene. These conditions were cystic fibrosis, classical congenital adrenal hyperplasia, autosomal recessive non-syndromic sensorineural deafness, familial Mediterranean fever and Alpha thalassaemia, among others.

Considerations

Current legal regulations accept that genetic knowledge is changing every day and establish that genetic screening for autosomal recessive genes known to be prevalent has to be done according to international scientific evidence. Nowadays the possibilities to screen are larger number of diseases than they were traditionally. Furthermore, professional guidelines open the possibility of assessing the inclusion of other genetic diseases in relation to the current state of knowledge and technological development so it seems reasonable to consider the incorporation of new tests to decrease the genetic risk when ART is performed. Nevertheless, there is some controversy about its implementation (9). ASEBIR recently announced its position statement on widened screening genetic tests of recessive diseases in OD programmes clarifying that at the present time genetic matching tests are not obligatory as there is no regulation that requires them. This document recommends informing the patients of the existence of these genetic studies and assessing case by case whether to do them. ASEBIR also consider recommendable to inform recipients that information about the donor’s genetic profile is available and, if it is asked for, giving them information of clinical relevance for the recipients and their offspring (12).

From our experience it seems clear that giving adequate information and personalized counselling, the introduction of an expanded carrier screening in an OD programme could have a very high implementation rate. The incorporation of a Genetic Counsellor is crucial for this process as genetic counselling is essential at different stages of the clinical process in order to transmit information of the genetic results to donors and recipients while decreasing the anxiety that they can generate.

According to our protocol, carriers for autosomal recessive conditions were not excluded, but the information was considered in the genetic-matching. Taking into account that we are all carriers of recessive mutations and that we are not trying to look for the best donor but to avoid matchings at risk, it seems disproportionate to exclude donors only for being carriers of some autosomal recessive disease, as has been previously recommended by scientific societies (9, 12).

The main objective of introducing this type of test in an OD programme was to identify carriers and to avoid matchings at risk for disorders that will severely affect children during early life. With the use of the qCarrier test we have decreased the risk of a newborn with a recessive genetic condition by 0.85% (10, 11). A detection rate of 3.5% of at-risk couples for a certain recessive condition is an extraordinarily high one, and the reduction of 0.85%, although modest, would represent approximately 3,500 newborns with a recessive condition in the Spanish population in 2016. According to our experience, the expanded carrier screening has proven to be helpful in identifying matchings with a high reproductive risk for transmitting a severe autosomal recessive condition to the offspring.

In our opinion, expanded carrier testing should be offered not only in the gamete donation context but also to all couples or persons of reproductive age, or to all assisted reproduction patients. We have already started to implement ECS in all reproductive contexts, including cou-
amples seeking spontaneous pregnancy or before IVF with own gametes.

References


