

First European baby free from Vanishing White Matter Disease

Baby Aina was born two years ago in Barcelona, free from the disease that had caused her brother's death. It is the first reported baby born from PGD for Vanishing White Matter Disease in Europe, and also the first worldwide report for EIF2B4 gene.

Families carrying genetic diseases can access this technique to prevent the transmission of the carrier gene.



At 21 months, Aina is the first baby born in Europe free of the Vanishing White Matter Disease (CACH, childhood ataxia with central nervous system hypomyelination), a hereditary, severe, progressive, and weakening disease that belongs to the group of leukodystrophies.

Her birth, recently presented at the 11th International Conference on Preimplantation Genetic Diagnosis, May 17-19, 2012 – Bregenz (Austria), has been possible due to the application of the Preimplantation Genetic Diagnosis technique carried out by the *Center*

for Embryo Medicine for ESIMER reproduction center, which treated the child's parents.

Leukodystrophies are a group of rare genetic diseases (estimated to affect less than 5 in every 10.000) that destroy the central nervous system (brain and spinal cord) and affect myelin (white matter that covers and isolates the nerves).

The Vanishing White Matter Disease is characterized by impaired coordination, balance, body and eyes movement, diction (ataxia), muscle stiffness, and restricted mobility (spasticity), optic atrophy leading to blindness, seizures, and

«Leukodystrophies are a group of rare genetic diseases that destroy the central nervous system (brain and spinal cord) and affect myelin»

in many cases death within few months from birth.

It belongs to the so-called “orphan diseases” since, even though they are progressive, debilitating, and very serious, only a limited number of patients are affected by it so there aren't enough adequate therapeutic strategies or resources destined by the pharmaceutical industry for its research.

Up until recently, carrier couples had to adopt children or else renounce to have any. Preimplantation Genetic Diagnosis now gives them the opportunity to have a healthy child, just like Aina.

Her parents had already had a child who passed away due to the disease

Aina's parents had had a first baby who was affected by the disease and died at almost two years of age. There had not been any other cases in the family. The baby was genetically studied and was found to have two mutations in EIF2B4 gene, one inherited from her mother and the other one inherited from her father. This disease has an autosomal recessive inheritance pattern, what means that only those who inherit two muta- ▶▶▶

►►► tions in the same gene can develop the disease, while those who have only one mutation (like each of Aina's parents) are asymptomatic carriers.

Aina's parents had a 25% risk of having an affected child in each of the following pregnancies, but did not even accept this risk. They did not wish to undergo a pregnancy termination in case a prenatal diagnosis revealed an affected fetus, either. That's why they decided to attend the ESIMER reproduction center in Barcelona, asking for an In Vitro Fertilization (IVF) with Preimplantational Genetic Diagnosis (PGD) which was performed by the Embryo Medicine Center.

Hope for couples with genetic diseases

IVF with PGD is a very specialised assisted reproduction technique where a multidisciplinary team composed of gynecologists, embryologists and molecular biologists must work together in a coordinate way and under strict deadlines. During the IVF cycle, several eggs from the patient are retrieved after hormone stimulation. These are fertilized with sperm from the couple and one cell of each embryo is biopsied on day 3 of development in order to perform the genetic analysis. Results are obtained on day 5, so that only those embryos that did not inherit the genetic disease are transferred to the maternal uterus. Couples that wish to avoid transmitting a genetic disease to their offspring through PGD have to undergo an assisted reproduction treatment although they do not have fertility problems, as the embryos must be generated and diagnosed before implantation. The success of this treatment depends on several factors such as



Testing the embryos for the mutation and the markers simultaneously is a more robust analysis than testing only for the mutation, and allows achieving a test reliability around 98%.



DNA extracted from the blood serves to analyse the chromosomal region where the involved gene lies and search for linked genetic markers that help characterize the different chromosomes and distinguish the mutated from the normal ones.



IVF with PGD is a very specialised assisted reproduction technique where a multidisciplinary team composed of gynecologists, embryologists and molecular biologists must work together in a coordinate way and under strict deadlines.

the maternal age, number and quality of retrieved eggs, number and quality of generated embryos, kind of disease (depending of mode of inheritance, one should theoretically expect more or less percentage of affected/non affected embryos), gynaecological condition of the patient, etc. Aina's parents went through three consecutive IVF cycles with PGD, after what they finally achieved what they were looking for, a healthy pregnancy.

PGD for other rare diseases

Aina's case is unique in the sense that it was not previously reported a PGD for this disease. Nevertheless and despite of its technical complexity, it is nowadays a standard procedure that can be applied almost to any single gene disorder, provided the responsible mutation is known in the family (proven with the corresponding genetic report) and there is at least another affected/carrier relative who can participate in the study (there are exceptions where PGD can be performed in the absence of other affected relatives, but each case must be evaluated separately to check feasibility).

Although the strategy is always similar for all the cases, PGD is personalised for each couple because the test is directed to detect the reported mutation(s) in the embryos of such specific couple. Therefore, it is always necessary to perform a set-up study (named "informativity study") prior to the IVF cycle. For this study, a blood sample is extracted from both members of the couple as well as from the participating relatives. DNA extracted from the blood serves to analyse the chromosomal region where the involved gene lies and search for linked genetic

markers that help characterize the different chromosomes and distinguish the mutated from the normal ones. Testing the embryos for the mutation and the markers simultaneously is a more robust analysis than testing only for the mutation, and allows achieving a test reliability around 98%. The work-up study is also needed to check the developed test in single cells. Once it is finished, patient can start hormone stimulation for IVF.

Spain, the European leader in PGD

Spain is the European country in which more cases of PGD are carried out, according to the PGD Consortium. Considering the Spanish Association for the study of Reproductive Biology's register, we find that more than 12 thousand have been carried out between 1993 and 2009. They are more by the day, as the gathered data shows: more cases have been carried out within the last two years in this time period than in the first twelve. To understand the volume of the activity, we must consider that PGD is not only carried out to prevent genetic diseases, it's also applied as a complementary technique in fertility treatments for infertile couples seeking to increase their chances of pregnancy. This last remark applies for the majority of cases, up to an 84%, an understandable amount considering maternity is increasingly postponed and seminal quality is decreasing, driving more and more couples to seek for medical help to have a child.

According to the same report by the Spanish Association for the study of Reproductive Biology, genetic illnesses motivate an 8% of the total cases of PGD, whose

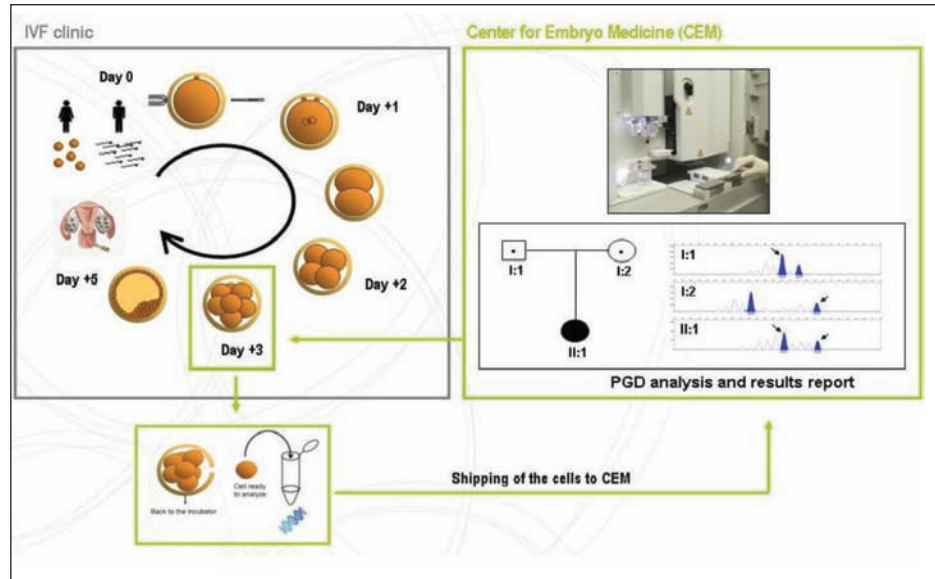


Figure I- Description of the IVF-PGD cycle.

results are increasingly encouraging: over 87% of these cycles conclude in embryo transfer, with pregnancy success rates over 35%.

The embryonic cell is sent from the couple's clinic to the Center for Embryo Medicine in Barcelona

While PGD in Spain is very advanced and allows to increase the chances of pregnancy of an In Vitro Fertilization cycle, in countries such as Italy, Germany, or Switzerland the technique remains forbidden by law. Thus, many affected couples must go abroad for treatment. In determined cases in which law forbids the use of the technique, patients must travel to another country for a solution. Nevertheless, in certain countries in which PGD is limited or in which there are not enough resources for it to be carried out as a routine in all centers, patients can access the technique without leaving their country. In these cases, only one cell of each embryo must travel to be analyzed.

«Spain is the European country in which more cases of PGD are carried out, according to the PGD Consortium».

The procedure is the following (Figure I): the affected couple goes to a reproduction clinic in their country, requesting treatment to have a child free from their disease. The clinic performs an In Vitro Fertilization and once it obtains the embryos, it sends a cell of each of the embryos to be analyzed to the Center for Embryo Medicine in this case. At the Center for Embryo Medicine we perform PGD and once we have the results, we send the encrypted diagnose to the clinic. With this information, the clinic can choose only the embryos free from the hereditary disease to transfer to the woman.

A window of hope gets opened for that family. Aina's case, as well as many others, has come to life free from her parents' genetic disease.

Esther Velilla
Center for Embryo Medicine
Director

