Press release
December 15, 2022

Sant Pau and Puigvert carry out the selection process of a compatible embryo and bone marrow transplantation into sickle cell anemia for the first time in this country

This has allowed a girl, Diama, only 11 years old and affected by this disease to make normal life

- **The two centers, St. Paul and Puigvert, have jointly carried out this process for an 11-year-old patient with this very serious hereditary genetic blood disease and frequent in people of African descent.**

- **The Reproductive Medicine Service of Fundació Puigvert–Sant Pau has been responsible for the in vitro fertilization process with genetic selection of an embryo not affected by the disease and immunologically compatible with the patient**

- **The Pediatric Service of Sant Pau performed a bone marrow and umbilical cord blood transplantation, based on a genetically selected sister of the patient**

Resource images and video: https://flic.kr/s/aHBqjAgxYQ

Barcelona, December 15, 2022.- The Hospital de la Santa Creu i Sant Pau and the Fundació Puigvert have been the first in Catalonia and in Spain to have carried out both the pre-implantation genetic diagnosis process with antigens of leucocytic histocompatibility (DGP-HLA, for its acronym in Spanish) and the transplantation of hematopoietic cells of umbilical cord blood and bone marrow from a genetically selected sister.

Sickle cell disease is a genetic disease that is inherited in a recessive way, which means that both parents have the gene that carries this pathology. More specifically, it is a group of red blood cell disorders that causes abnormal hemoglobin production and can cause many medical complications in different organs of the body and infections due to poor perfusion and oxygenation of tissues. This disease deforms red blood cells causing chronic anemia and hindering blood circulation, leading to vascular obstructions and microinfarcts in different organs, including stroke. These patients present very intense acute pain episodes and have a

limited life expectancy between 40 and 50 years. The only healing treatment at present is hematopoietic cell transplantation of an unaffected donor. This has been the case with the Diama, since both parents are carriers of the gene that causes this disease.

According to **Dr. Isabel Badell**, director of the hematopoietic transplant unit of the Pediatric Service of Sant Pau, "*this is another step within the expertise and innovation of the Hospital in the field of transplants, where we are pioneers since1976, when we did the first bone marrow transplant in Spain*". In fact, the doctor was already part of the team of professionals who carried out this first transplant and since then more than 600 have been made in children at the Hospital de Sant Pau, being a national and international reference in this area.

Dr. Ana Polo, director of the Reproductive Medicine Service of the Fundació Puigvert – Sant Pau, explains what it means to make a Preimplantation Genetic Diagnosis (PGD): *"PDG is a technique of assisted reproduction that consists in detecting genetic and/or chromosomal abnormalities in embryos obtained in vitro for the subsequent transfer of those considered as "healthy" by the pathology sought in the maternal uterus."*

The Fundació Puigvert initiated the PGD Program in 2001, and since then, it has been growing and has been consolidated as one of the most important in Spain within public health with a accumulated experience of more than 600 cases.

As of 2006 and coinciding with the new law on assisted human reproduction techniques, the Catalan Health Service accredited the Fundació Puigvert for being a reference center for selection of unaffected embryos and HLA compatible (cases where a sick brother or sister requires a bone marrow transplant).

*"These are complex cases that require a multidisciplinary focus with the participation of different specialists: Pediatrician, gynecologist, andrologist, geneticist, embryologist, among others"*as **Dr. Polo** tells us.

The parents of the Diama wanted another gestation and were referred to the Hospital de Sant Pau derived by their pediatrician, **Dr. Marta García-Bernal**, to assess the case in November 2015. From the Pediatrics service, **Dr. Badell** explained to them that the PGD with HLA and subsequent bone marrow transplantation was the best therapeutic option.

In February 2016, the couple underwent an evaluation at the Reproductive Medicine Service. They were explained the previous study that had to be carried out, the procedures, the circuits and the success rate of the techniques: Both PGD with HLA and transplant.

Medical tests were requested to see if it was appropriate to perform a PGD cycle with HLA in its case. The woman has to be of a suitable age for the success of the technique: in this case, she was 26 years old and she had a correct ovarian reserve evaluated by hormonal analysis and transvaginal ultrasound. In this patient, the ovarian reserve was also high and her partner had a normal seminal assessment.

In these cases it is important to carry out a good reproductive advice and an extensive explanation about the technique, its possible complications and the prognosis without false expectations, since the gestation rate of the PGD is 45-50%, but this success rate decreases considerably if a PGD with HLA is necessary, since the probability of obtaining a "non-ill"

embryo for a recessive hematological condition is 75% (3/4), the probability of obtaining a compatible HLA embryo is 25% (1/4) and, therefore, in this specific case the probability of obtaining a sa embryo for sickle cell disease and HLA-compatible with an affected sibling is 18% (3/4 x 1/4= 3/16). That is, out of every 10 embryos, only 1 or 2 will be "fit" for implantation. But, besides having these 2 genetic requirements, it had to be a chromosomically normal embryo.

"Once the couple were considered fit for treatment, they made a visit with Dr. Olga Martínez, an embryologist responsible for the cases of PGD of the Fundació Puigvert, to explain the most technical part of the procedure and the need for authorization from the National Commission for assisted Human reproduction (CNRHA, for its acronym in Catalan) (mandatory in cases of PGD to cure sick or therapeutic siblings) ", as **Dr. Polo** tells us.

According to **Dr. Badell**, "*today there are several treatments, but the only curative is the transplantation of bone marrow or umbilical cord stem cells of a compatible person, with a disease-free survival rate of more than 80%, especially if it is from a sibling.*" Here, the PGD is essential "*to study, apart from the disease and HLA typing, chromosomal and genetic abnormalities in the embryos obtained in vitro and the transfer to the maternal uterus of the healthy and compatible embryo for the pathology analyzed".*

It is important to indicate the procedure of DGP-HLA and transplants in an early phase of the disease before serious complications of pathology occur. Treatment is long and difficult. In the case of the mother of Diama, three cycles of ovarian stimulation took place until finding an embryo that met the two essential requirements to carry it out. First, being free of the gene that causes sickle cell disease. And, second, that the genes of the immune system were compatible with those of the patient, what is called histocompatibility antigens (HLA).

Three cycles of fertilization and only a single embryo that met the requirements

The situation of Diama when she arrived at the Hospital de Sant Pau was very serious, with multiple vessel-occlusive crises, characterized by episodes of acute pain that required analgesics, including morphine based. Despite medical treatment, the patient needed frequent hospitalizations and periodic transfusions. According to **Dr. Badell**, *"the only definitive treatment in this case was the transplant of bone marrow."*

In total, more than six years have passed since the arrival of the Diama and her parents in Sant Pau until the day of the transplant. The chronology, broadly speaking, has been the following:

- November 2015: The parents of Diama arrive at Sant Pau derived by their pediatrician, Dr. Marta García-Bernal, with the desire for a new gestation and to assess whether any intervention could be carried out that helped her ill daughter.

- Their medical suitability for this treatment is confirmed and they are explained the procedure to be followed by Pediatrics and Reproductive Medicine.

- March 2016: Authorization is requested to make a PGD with HLA for therapeutic purposes for third parties to the National assisted Human reproduction Commission (CNRHA), who in the same year dictates a favorable resolution.

- February 2017: First hormone stimulation treatment. 24 eggs are obtained, 9 embryos are biopsied: 1 is non-carrier, but also not HLA compatible, 2 embryos are healthy carriers, but not HLA compatible, and 6 embryos are unfit. 6 embryos are discarded and 3 are frozen, but none of them meet the 2 requirements (without illness and compatible HLA) to be implanted.

- October 2017: Second hormone stimulation treatment. Despite having obtained 15 eggs, only 3 embryos that are frozen without biopsies develop correctly because they are very few and there is a good chance that there are none that are unaffected and HLA compatible.

- April 2018: Third hormone stimulation treatment and obtaining 30 oocytes: 26 are mature and they are frozen. 22 survive, 17 are fertilized and, on the 5 day of embryonic development, 5 embryos are obtained.

- From there, 3 embryos of the second cycle (October 2017) and 5 of the third hormone stimulation cycle (April 2018) are analyzed, with these results: 2 embryos are not transferable, 2 embryos are affected, 3 embryos are non-carriers, but are not HLA compatible, and 1 embryo is non-carrier and is HLA compatible.

This last embryo that has the essential requirements is implanted in the mother of Diama in October 2018, giving rise to a pregnancy that develops without complications. In September 2019, a baby girl, Sokna, is born and the blood from the umbilical cord is collected. But unfortunately, this cord blood had insufficient cellularity and it was necessary to proceed with a bone marrow extraction in two times (in March and May 2021) in the donor sister.

Subsequently, Diama had to undergo a chemotherapy treatment to eliminate her bone marrow before the transplantation of the cells from her little sister, so that she did not reject them. Transplant was performed in April of this year by presenting a good evolution with implant onset at seven days and it is verified that the bone marrow has been successfully implanted. The patient is free of symptomatology from that date.

But the story does not end here, since in July 2021, the parents of Diama decided that they want to have more children. Thus, two embryos obtained in the above procedure not affected and not compatible with HLA are transferred to the mother. On July 21, 2022, Mouhamed and Aisha were born, two twin brothers to fulfill the parents' desire to increase the family.

On the PROGRAM FOR ASSISTED REPRODUCTION (PRA, by its acronym in Catalan) of the HOSPITAL SANT PAU-FUNDACIÓ PUIGVERT

The Program for assisted reproduction (PRA) of the Hospital Sant Pau-Fundació Puigvert established in 1985 is the result of the alliance of the two institutions and the respective services of Andrology and Gynecology, leaders in the knowledge and clinical practice of assisted human reproduction, with an integral focus of a health problem that affects, by concept, couples.

Pioneer in Catalonia and a benchmark at the state level, the PRA was the first program of Catalan public healthcare to create a semen bank and carry out inseminations with semen of donor as well as preservation of male fertility due to medical reasons (cancer patients).

In 1987 it achieved the first pregnancy through In Vitro Fertilization (IVF) of the Catalan public healthcare.

At the moment the PRA performs more than 1.000 cycles of artificial insemination and more than 800 FIV's in the various modalities.

In the present case, the Preimplantation Genetic Diagnosis (PGD), the Hospital de Sant Pau and the Fundació Puigvert were also pioneers in 2002 in including this technique in their assisted reproduction program in the field of public health.