
ISSN: 3068-8965
Journal of Pediatric Advance Research

ATHENAEUM SCIENTIFIC PUBLISHERS

Case Report

Transfusion-Dependent Thalassemia in a Donor-Conceived Infant

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Citation: Jondhale SN, et al. Transfusion-Dependent Thalassemia in a Donor-Conceived Infant. J Pediatric Adv Res. 2025;4(3):1-6.

http://dx.doi.org/10.46889/JPAR.2025.4309

Received Date: 13-11-2025

Accepted Date: 03-12-2025

Published Date: 10-12-2025

Abstract

Transfusion-Dependent Thalassemia (TDT), a severe form of inherited hemoglobinopathy, is caused by mutations in the genes responsible for hemoglobin synthesis. Genetic carrier screening is a standard practice for couples planning a family and is especially critical in Assisted Reproductive Technology (ART) involving donor gametes to prevent the transmission of genetic disorders. This case report details a rare and unexpected case of Transfusion-Dependent Thalassemia (TDT) in a 4-month infant conceived through *In-vitro* Fertilization (IVF) using donor gametes. The biological parents were phenotypically normal and non-carriers, but the donor was not screened for hemoglobinopathy. The case underscores the urgent need for mandatory genetic screening of gamete donors in Assisted Reproductive Technologies (ART), especially in regions with high prevalence of hemoglobinopathy.

Keywords: Transfusion-Dependent Thalassemia; Assisted Reproductive Technology; *In-vitro* Fertilization

Introduction

Thalassemia is an autosomal recessive inherited blood disorder that affects hemoglobin, the protein in red blood cells that carries oxygen. It's a type of hemoglobinopathy characterized by ineffective red blood cell production, which leads to lifelong dependence on blood transfusions. These frequent transfusions can cause iron overload, leading to damage in various organs [1-3].

Living with thalassemia major involves more than just frequent blood transfusions and the associated stress. Patients and their families often face social stigma and isolation due to a lack of understanding within their communities. The ongoing requirement for transfusions every 15-20 days, coupled with the necessity of iron chelation therapy, imposes a substantial financial and social burden on affected families as well as the broader healthcare system [4-6]. The only cure for thalassemia major is a Bone Marrow Transplant (BMT), which is expensive and requires a matching donor. Genetic carrier screening is a standard practice for couples planning a family and is especially critical in Assisted Reproductive Technology (ART) involving donor gametes to prevent the transmission of genetic disorders [7].

Case Presentation

An infant was brought to the pediatric outpatient clinic with a 2-week history of progressive pallor, irritability and poor weight gain. There was no history of bleeding from any site and jaundice. Child does not have diarrhea and fever. On examination child temp was normal with HR of 132/min and RR-40/min. Weight was 4.9 kg, lengh-59 cm and head circumference 38 cm. There was severe pallor present. No icterus, edema or lymph adenopathy. Systemic examination revealed spleen 3 cm without hepatomegaly. Other systemic examination was normal. The infant was born at term with a normal birth weight and no perinatal complications. He had jaundice at Day 10 of life for which he received phototherapy. There was no consanguinity in the family and parents were non-consanguineous, clinically normal and no family history of thalassemia.

Initial evaluation revealed profound anemia, with hemoglobin at 3.5 g/dL, accompanied by Microcytic (MCV 65 fL), Hypochromic (MCH 20 pg) indices and an elevated reticulocyte count of 8%. Total serum bilirubin was 4.2 mg/dL, with a direct fraction of 1.1 mg/dL. Peripheral smear demonstrated marked anisopoikilocytosis, microcytosis, hypochromia and numerous target cells. High-Performance Liquid Chromatography (HPLC) showed Hb F at 98.7%, Hb A absent (0%) and Hb A_2 at 1.3%-a pattern highly suggestive of beta thalassemia major.

While differential diagnoses for neonatal anemia-including hemolytic disease of the newborn (Rh/ABO incompatibility), congenital infections and rare hereditary anemias such as Diamond-Blackfan anemia-were considered, the constellation of microcytic hypochromic indices and elevated fetal hemoglobin on HPLC strongly supported a diagnosis of Transfusion-Dependent Thalassemia (TDT).

A diagnostic surprise emerged when both parents were found to have normal HPLC profiles ($HbA_2 < 3\%$), raising immediate questions about the etiology of transfusion-dependent thalassemia in their child. Upon further inquiry, the parents disclosed that the infant had been conceived via *In-vitro* Fertilization (IVF) using anonymous donor gametes. Crucially, they were unaware of any genetic screening protocols applied to the donors. Due to technical and legal constraints, the thalassemia carrier status of the donors could not be verified. Subsequent molecular analysis of the infant revealed a homozygous IVS-I-5 (G>C) mutation in the beta-globin gene, consistent with classical beta thalassemia major.

Child was given Rh typed ABO and extended phenotype compatible blood transfusion in small aliquot (5 ml/kg) for 3 days due to severe anemia with target hemoglobin 9-10.5 gm/dl. Parents were counseled for 3 weekly blood transfusions to keep target hemoglobin and iron overload in future requiring iron chelation therapy. The family was counseled on the long-term management including the possibility of a definitive cure through hematopoietic stem cell transplantation at 2-3 years of age as per availability of donor match.

Discussion

Thalassemia is an inherited blood disorder caused by defects in the genes responsible for producing hemoglobin. Transfusion Dependant B Thalassemia (TDT) is the most severe form, characterized by a complete absence of β-globin production. India has the highest number of people with thalassemia major globally and is often referred to as the "Thalassemia capital of the world". With an estimated 50 million beta-thalassemia carriers, the country contributes to approximately 25% of all new cases reported worldwide. More than 10,000 new cases are diagnosed annually [1,2].

The financial burden of TDT is immense, involving regular blood transfusions every two to four weeks, costly iron chelation therapy to manage iron overload and the constant threat of organ damage. In this context, the diagnosis of a severe, life-long genetic disorder such as Transfusion-Dependent Thalassemia (TDT) in an infant conceived from donors presents a profound and tragic paradox. The diagnosis had profound emotional and financial implications for the family, who had believed they had taken all necessary precautions. There is a significant global disparity in care, with patients in low- and middle-income countries often lacking access to adequate blood supply, chelation drugs and comprehensive care, leading to reduced life expectancy and higher mortality rates [2].

Confirmation of diagnosis of such case is also not an easy task as parents often hesitate to disclose pregnancy details involving *In-vitro* Fertilization (IVF). If both the parents are not carrier and child is affected with hemoglobinopathy then either child is adopted or born with IVF. To confirm the diagnosis and investigate the source of the mutation, genetic testing for HbB Mutations needs to be performed. The infant in our case was found to be homozygous for the IVS-I-5 (G>C) mutation in the HBB gene, a common mutation causing β-thalassemia [3,4].

Although in our case infant's condition stabilized with regular blood transfusions and he showed improvements in feeding and activity. Long-term follow-up is needed in a specialized pediatric hematology clinic to monitor for complications such as iron overload and to evaluate potential transplant options. Transplantation represents the only curative treatment for Transfusion-Dependent Thalassemia (TDT), offering a permanent solution to a life-long illness. In the absence of an HLA-matched sibling donor as well parents, parental decision-making around hematopoietic stem cell transplantation becomes particularly complex. Also achieving a successful transplant outcome in such scenarios remains a significant clinical challenge [5-7].

The standard practice for most donor banks for IVF is to test for infectious diseases and a limited panel of genetic conditions. However, the sheer number of possible thalassemia mutations makes comprehensive screening challenging. It's possible for a donor to be a carrier for a rare mutation that is not included in the standard screening panel. Thalassemia is an autosomal recessive disorder, meaning a child can be affected only if they inherit a mutated gene from both parents. In a donor-conceived pregnancy, this requires both the sperm and egg donors to be carriers for a thalassemia gene [8].

This case reveals a systemic oversight in ART protocols where donor gametes were not screened for hemoglobinopathy. Despite both parents being non-carriers, the child inherited a homozygous β-thalassemia mutation from the donor. The fact that a child was born with the condition indicates that both donors were carriers of a pathogenic variant which should have been identified if donors were screened. In high-prevalence regions like South Asia, this poses a significant risk. In case where donor's evaluation is not done then Preimplantation Genetic Testing (PGT) technique can be used to identify genetic defects in embryos created through *In-vitro* Fertilization (IVF) before pregnancy [8,9].

This is the probably only documented case of transfusion-dependent thalassemia in an IVF-Conceived Infant from Donors. The incident demands urgent introspection and reform across multiple fronts like standardized and comprehensive genetic screening protocols, transparent informed consent along with clear legal and ethical guidelines to delineate responsibility especially for high-prevalence conditions like hemoglobinopathy

Conclusion

A baby was born with a severe, lifelong condition called thalassemia, which requires regular blood transfusions, even though the pregnancy was conceived using a sperm or egg donor. This isn't just a sad medical story-it points to a serious flaw in the system. This case shows that our current reproductive technologies don't have all the necessary safety checks in place. The failure was a rare but critical mistake in the genetic screening of the donor, leading to a preventable genetic disorder. It highlights a deeply human tragedy and the urgent need to close these gaps. Ultimately, solving this problem will take a team effort. Geneticists, fertility doctors, public health experts and lawmakers must all work together to make sure that the advancements in modern medicine don't accidentally create new health challenges for future generations.

Conflict of Interests

The authors declare that they have no conflicts of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or non-profit sectors.

Author Contributions

All authors contributed equally.

Consent Statement

The informed consent has been obtained and the patient anonymity preserved.

Data Availability Statement

Data and Materials are available from the authors upon reasonable request.

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