

Replacement Therapy for Gaucher Disease during Pregnancy: A Case Report

Stefano Raffaele Giannubilo*, Angela Pasculli, Elisa Tidu, Andrea Ciavattini

- Department of Clinical Sciences, Polytechnic University of Marche, Ancona, Italy

* Corresponding Author:

Stefano R. Giannubilo,
Department of Clinical
Sciences, Polytechnic
University of Marche
at Salesi Hospital via F.

Corridoni 11

60123 Ancona, Italy

E-mail:

s.giannubilo@univpm.it

Received: Jul. 6, 2014

Accepted: Sept. 23, 2014

Abstract

Background: Gaucher disease is a lysosomal storage disorder due to deficiency of glucocerebrosidase enzyme. In this study, a case of enzyme-treated woman during her pregnancy was reported.

Case Presentation: A 27-year old woman with type I Gaucher disease was managed for pregnancy until delivery. She underwent elective splenectomy at age 26 years and was treated with 19-38 units/kg of imiglucerase. A conservative approach with close monitoring of both mother and baby was planned.

Results: In the 39th week of pregnancy, a healthy male baby of 3180 g was delivered via cesarean section.

Conclusion: Apart from mild hematological complications, the pregnancy, the delivery and the puerperium were uneventful. In this case report, the issue of therapy and risk assessment in pregnancy in patients with type I Gaucher disease was discussed.

Keywords: Delivery, Gaucher disease, Imiglucerase, Pregnancy, Splenectomy.

To cite this article: Giannubilo SR, Pasculli A, Tidu E, Ciavattini A. Replacement Therapy for Gaucher Disease during Pregnancy: A Case Report. *J Reprod Infertil.* 2015;16(1):53-57.

Introduction

Gaucher disease is an autosomal-recessive lysosomal storage disorder caused by mutations in the gene encoding acid beta-glucosidase (GBA1). The decreased enzymatic activity leads to accumulation of glucocerebroside within characteristic "Gaucher cells" of mononuclear phagocyte origin identified in most tissues. The disease occurs in three clinical forms. Type 1 (adult) is by far the most common type; it is characterized by accumulation of glucocerebroside in the spleen, liver, and bone marrow and by sparing of the central nervous system. Type 2 (infantile) and type 3 (juvenile) are the two rare neuropathic forms.

Type I disease affects 1 in 50.000-100.000 people worldwide and 1 in 400-600 people among Ashkenazi Jewish population (1). Few data on the frequency of Gaucher disease during reproductive age and pregnancy can be found in the literature and prevalent data have been reported in The Netherlands (2 per 100,000 live births), in Australia (1 per 57,000 live births) and Portugal (3 per 100,000 live births) (2). Pregnancy concurrent

with Gaucher disease may have several problems, not only by exacerbation of existing signs and symptoms but also by triggering new features (3), which may incur additional risk of complications such as changes in haematological parameters (4), postpartum infection (5), antepartum or postpartum bleeding due to platelet aggregation (6), and bone disease (3). Specific therapy for the non-neuronopathic manifestations of Gaucher disease has been available since 1991 firstly in the form of the macrophage targeted placenta-derived glucocerebrosidase (alglucerase, Ceredase®, Genzyme Corporation, MA) (7), and subsequently (1994 in USA and 1997 in Europe) by recombinant human enzyme, imiglucerase (Cerezyme®, Genzyme Corporation, MA) (8).

Substrate reduction therapy (miglustat, Zavesca®; Actelion Pharmaceuticals, Allschwill, Switzerland) has more recently been licensed for type 1 of Gaucher disease in adult patients with mild to moderate disease for whom enzyme replacement therapy with imiglucerase is not a therapeutic op-

tion (9-11). Imiglucerase has a pregnancy category C rating from the Food and Drug Administration (FDA) with the warning that "it is not known whether it is harmful to an unborn baby" and with the indication that treatment should be provided to pregnant women only if "clearly needed".

Case Presentation

In this report, the case of a 27-year-old Italian woman (height, 164 cm; weight, 55 kg) was presented during the second month of her first pregnancy. She had no history of illness until 25 years of age, when she developed general fatigue and bleeding tendency and the symptoms led to diagnosis of Gaucher disease. The diagnosis was based on anemia, thrombocytopenia, elevated levels of serum acid phosphatase and angiotensin-converting enzyme, hepatomegaly, splenomegaly, the presence of Gaucher cells in bone marrow aspiration. No other family members were suffering from the disease. DNA analysis of the GBA gene revealed that she was heterozygous for the c.1448T>C (p.L444P) mutation. The treatment for the patient started with 19-38 units/kg of imiglucerase (Cerezyme; Genzyme, MA, USA) every two weeks. The patient underwent elective splenectomy at age 26 years for massive splenomegaly. Menorrhagia improved, hemoglobin concentration and platelet count normalized, biomarkers of disease (chitotriosidase, acid phosphatase, and angiotensin-1-converting enzyme) improved, and liver volumes decreased. The patient became pregnant at 27 years of age and, with informed consent, continued imiglucerase treatment throughout all pregnancy, as previously described (12) at Salesi Mother and Child Teaching Hospital of Ancona (Italy) in the year 2012. Genetic counseling was performed at the first obstetric examination and a prenatal testing for Gaucher disease and amniotic fluid sampling (16th week) were carried out, thereby, the existence of the disease and other chromosomal anomalies was excluded.

By the second month of pregnancy, monthly obstetric ultrasound and blood sampling were performed and by week 20 of gestation bi-weekly determinations of blood counts revealed that hemoglobin levels were ranging from 9.8 to 10.9 g/dl and platelet counts from 96,000 to 135,000/mm³. The prothrombin time and partial thromboplastin time were normal. The biophysical profile studies, as well as Doppler analysis, were repeated every two weeks in outpatient clinic of our teaching

hospital. In the 39th week of pregnancy, an elective cesarean section on maternal choice was carried out and a male baby of 3180 g was delivered. Epidural anesthesia was chosen with nasal oxygen throughout. No adverse neonatal outcomes and no congenital anomalies were registered. An uneventful recovery period was observed and the patient was discharged on the 4th postoperative day. No postoperative complications were observed after delivery. X-ray examination after delivery revealed no bone abnormalities and finally no further increase in the size of the patient's spleen was observed. The patient decided not to breastfeed.

This study was approved by the local departmental ethics committee and written informed consent was obtained from the patient for the case report to be published.

Discussion

The signs and symptoms of Gaucher disease may have an impact on pregnancy and birth, particularly hepatosplenomegaly may be massive and may alter the normal growth in pregnancy; anemia and thrombocytopenia may be exacerbated by pregnancy and the bleeding tendency may be mild in a nonpregnant patient but may become critical during birth. On the other hand, pregnancy may affect the course of Gaucher disease, with regard to signs and symptoms that existed previously as well as the possibility of triggering new features, *i.e.* bone pains.

The ability of enzyme therapy to rapidly stabilize the disease, especially hematological parameters, has been reported previously (13).

There is accumulating evidence that replacement therapy with imiglucerase during pregnancy might stabilize the patient's condition for physiological changes of pregnancy, and reduce the incidence of complications during delivery and the postpartum period (11, 12, 14). The treatment has been related to a reduced risk of spontaneous abortion in women treated with alglucerase and/or imiglucerase, reduced risk of Gaucher-related complications during delivery, and a reduced risk of Gaucher-related complications during the postpartum period (11). The first antenatal appointment should include a comprehensive assessment of patient, drafting a birth plan, and a multidisciplinary approach to management of pregnancy in such a way that assessment should ideally be performed in a center with experienced experts in pregnancy management. Genetic counseling is recommended and indications for prenatal diagnosis should be

explained to the patient. For example, the facts about whether Gaucher disease mutations in one of parents are associated with a risk of neuropathic Gaucher disease and the other parent is a carrier of unknown genotype should be explained thoroughly (15). Monitoring in pregnancy should be adapted to the needs of the individual patient based on the disease status. Clinicians are advised to concentrate on direct parameters of Gaucher disease status, such as platelet count and platelet function that could affect patients during pregnancy and delivery. Ferritin concentrations are often elevated in the serum of Gaucher patients as part of the sustained acute inflammatory response (16). This usually does not indicate iron overload but may mask the presence of iron deficiency especially in pregnancy. Iron supplementation is advisable in pregnant Gaucher patients with hypochromic microcytic anaemia who do not have evidence of a haemoglobinopathy (*e.g.* β thalassaemia trait), reduced concentrations of serum iron and decreased serum transferrin saturation.

Even when most of the patients with Gaucher disease underwent splenectomy before the reproductive period, a reversible massive progressive splenic enlargement during pregnancy occurred (17).

Accumulated data presented here provide no evidence of any teratogenic effects even when given in the first trimester of pregnancy. Imiglucerase and alglucerase are generally well tolerated in Gaucher patients and have an excellent safety record (18). Pharmacovigilance data shows that imiglucerase is also well tolerated in pregnant women and there is no evidence of any adverse events specifically related to pregnancy (11).

Even if vaginal delivery is preferred and there is no specific indication for caesarean section, often a surgical delivery is preferred for the risk of splenic rupture during labor. Caesarean sections in Gaucher patients are more likely to occur because of disease profile of patients, such as orthopaedic considerations, rather than acute complications during delivery. Caesarean sections cannot alone be perceived as an indication of risk of complications, as these are increasingly carried out without medical indication at maternal request or because of caution on the obstetrician's part, despite associated risks (11).

Although hemorrhagic tendency may be observed in such patients (15), the state could be successfully managed conservatively, for example, by a low transversal Yoel-Cohen incision or a Pfannen-

stiel curved incision. Surgeons should avoid exploration of the peritoneal cavity unless there is a surgical indication, as palpation of enlarged organs in Gaucher disease may precipitate bleeding.

Because Gaucher disease is a disease with multi-organic involvement, preoperative assessment should be carried out in order to determine the extent to which the different organs are affected. General anesthesia should be avoided because of maternal aspiration syndrome and the risk of neurological and respiratory depression in the newborn. The use of regional anesthesia for patients with Gaucher disease undergoing surgery remains controversial; however, some authors point out that local anesthetics, as for cesarean section, may be safe provided that no other formal contraindications for their use is present, such as clotting parameter alterations, severe spinal deformities or spinal cord abnormalities, that would put the patient at risk of neurological sequelae (19, 20).

Perinatal demise of the newborn affected by Gaucher disease is very rare and is considered a variant of type 2 Gaucher disease that occurs in the neonatal period. The most frequent features are non-immune hydrops fetalis, in utero-fetal demise, and neonatal distress. In some cases without hydrops, neurological signs occur in the first week of life and lead to death within 3 months and some common signs of the disease are hepatosplenomegaly, ichthyosis, arthrogryposis and facial dysmorphism (21).

Few data to date are available on patients with Gaucher disease treated with imiglucerase during the lactation period, on its excretion into human breast milk and its effects on the newborn (22, 23).

Even when during breastfeeding, the enzyme was likely to be digested in the child's gastrointestinal tract suggesting minimal risk to infants (24), a continued healthy development of children breastfed by alglucerase or imiglucerase treated mothers has been reported (25). The European Medicines Agency and the US Food and Drug Administration indicate that caution should be exercised when imiglucerase is administered in nursing women. Postpartum, bone mineral density assessment using DEXA should be considered in cases of prolonged breastfeeding and checked at appropriate intervals after breastfeeding is completed.

Conclusion

The characteristics of the present case have many similarities with the ones stated in the litera-

ture since no significant complication occurred during the pregnancy and delivery. Although a mild anemia and thrombocytopenia was observed in the antenatal period, no transfusion was required.

Knowing the mechanism of autosomal recessive inheritance, especially in most severe forms, a prenatal diagnosis using amniocentesis or chorionic villus sampling should be offered to the patient. Having reviewed the related literature, it seems that if the disease is controlled, with proper therapy and monitoring, mothers are more likely to experience uncomplicated pregnancies and deliveries.

Conflict of Interest

The authors declare that there is no conflict of interests.

References

1. Cox TM, Schofield JP. Gaucher's disease: clinical features and natural history. *Baillieres Clin Haematol.* 1997;10(4):657-89.
2. Pinto R, Caseiro C, Lemos M, Lopes L, Fontes A, Ribeiro H, et al. Prevalence of lysosomal storage diseases in Portugal. *Eur J Hum Genet.* 2004;12(2): 87-92.
3. Granovsky-Grisaru S, Aboulafia Y, Diamant YZ, Horowitz M, Abrahamov A, Zimran A. Gynecologic and obstetric aspects of Gaucher's disease: a survey of 53 patients. *Am J Obstet Gynecol.* 1995;172(4 Pt 1):1284-90.
4. Elstein Y, Eisenberg V, Granovsky-Grisaru S, Rabinowitz R, Samueloff A, Zimran A, et al. Pregnancies in Gaucher disease: a 5-year study. *Am J Obstet Gynecol.* 2004;190(2):435-41.
5. Zlotogora J, Sagi M, Zeigler M, Bach G. Gaucher disease type I and pregnancy. *Am J Med Genet.* 1989;32(4):475-7.
6. Gillis S, Hyam E, Abrahamov A, Elstein D, Zimran A. Platelet function abnormalities in Gaucher disease patients. *Am J Hematol.* 1999;61(2):103-6.
7. Barton NW, Brady RO, Dambrosia JM, Di Bisceglie AM, Doppelt SH, Hill SC, et al. Replacement therapy for inherited enzyme deficiency--macrophage-targeted glucocerebrosidase for Gaucher's disease. *N Engl J Med.* 1991;324(21):1464-70.
8. Grabowski GA, Barton NW, Pastores G, Dambrosia JM, Banerjee TK, McKee MA, et al. Enzyme therapy in type 1 Gaucher disease: comparative efficacy of mannosyl-terminated glucocerebrosidase from natural and recombinant sources. *Ann Intern Med.* 1995;122(1):33-9.
9. FDA: Drug Approval Package [Internet]. Silver Spring: Food and Drug Administration; c1998-2002. Center for drug evaluation and research, approval letter, application number 21-348; 2003 Jul 7 [cited 2007 Jul 31]; [about 2 screens]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-348_Zavesca.cfm
10. EMA: Committee for Proprietary Medicinal Products [Internet]. London; European Medicines Agency; c1995-2012. Committee for Medicinal Products for Human Use (CHMP); 2012 Feb 20 [cited 2012 Feb 20]; [about 3 screens]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Summary_for_the_public/human/000435/WC500046724.pdf.
11. Zimran A, Morris E, Mengel E, Kaplan P, Belmatoug N, Hughes DA, et al. The female Gaucher patient: the impact of enzyme replacement therapy around key reproductive events (menstruation, pregnancy and menopause). *Blood Cells Mol Dis.* 2009;43(3):264-88.
12. Elstein D, Granovsky-Grisaru S, Rabinowitz R, Kanai R, Abrahamov A, Zimran A. Use of enzyme replacement therapy for Gaucher disease during pregnancy. *Am J Obstet Gynecol.* 1997;177(6): 1509-12.
13. Weinreb NJ, Charrow J, Andersson HC, Kaplan P, Kolodny EH, Mistry P, et al. Effectiveness of enzyme replacement therapy in 1028 patients with type 1 Gaucher disease after 2 to 5 years of treatment: a report from the Gaucher Registry. *Am J Med.* 2002;113(2):112-9.
14. Cox TM, Aerts JM, Belmatoug N, Cappellini MD, vom Dahl S, Goldblatt J, et al. Management of non-neuronopathic Gaucher disease with special reference to pregnancy, splenectomy, bisphosphonate therapy, use of biomarkers and bone disease monitoring. *J Inherit Metab Dis.* 2008;31(3):319-36.
15. Grabowski GA. Gaucher disease: considerations in prenatal diagnosis. *Prenat Diagn.* 2000;20(1):60-2.
16. Laine F, Guyader D, Turlin B, Moirand R, Deugnier Y, Brissot P. [Hyper-ferritinemia and Gaucher disease]. *Gastroenterol Clin Biol.* 1996;20(5):512-3. French.
17. Young KR, Payne MJ. Obstetric aspects of Gaucher's disease. *Br J Obstet Gynaecol.* 1985;92(9):993.
18. Starzyk K, Richards S, Yee J, Smith SE, Kingma W. The long-term international safety experience of imiglucerase therapy for Gaucher disease. *Mol Genet Metab.* 2007;90(2):157-63.
19. Houlton MC, Jackson MB. Gaucher's disease and pregnancy. *Obstet Gynecol.* 1978;51(5):619-20.

20. Dell'Oste C, Vincenti F. Anaesthetic management of children with type II and III Gaucher disease. *Minerva Pediatr.* 1997;49(10):495-8.
21. Brown DL, Wedel DJ, editors. Spinal, epidural and caudal anesthesia. New York: Churchill Livingstone Inc; 1990. 1377 p. (Miller RD, editor. Anesthesia; vol?).
22. Brown DL, Wedel DJ, editors. Spinal, epidural and caudal anesthesia. New York: Churchill Livingstone Inc; 1990. 1377 p. (Miller RD, editor. Anesthesia; vol. 25).
23. Sekijima Y, Ohashi T, Ohira S, Kosho T, Fukushima Y. Successful pregnancy and lactation outcome in a patient with Gaucher disease receiving enzyme replacement therapy, and the subsequent distribution and excretion of imiglucerase in human breast milk. *Clin Ther.* 2010;32(12):2048-52.
24. Mrcic M, Fumic K, Vrcic H, Kristina Potocki, Ranka Stern-Padovan, Maja Prutki, et al. Successful pregnancy on enzyme replacement therapy with cerezyme. *Clin Ther.* 2007;29:S84-S85.
25. Aporta Rodriguez R, Escobar Vedia JL, Navarro Castro AM, Aguilar Garcia G, Cabrera Torres A. Alglucerase enzyme replacement therapy used safely and effectively throughout the whole pregnancy of a Gaucher disease patient. *Haematologica.* 1998;83(9):852-3.