EJCRIM
European Journal
of Case Reports
in Internal Medicine

SUCCESSFUL PREGNANCY OUTCOME IN PATIENT WITH POMPE DISEASE DESPITE DISCONTINUATION OF ENZYME REPLACEMENT THERAPY

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Received: 16/04/2025
Accepted: 22/04/2025
Published: 21/05/2025

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: Written informed consent for the publication of her clinical data was obtained from the patient.
Acknowledgments: We would like to thank the staff of Division for Metabolic Diseases and the Clinic for Women's Diseases and Childbirth, whose support enabled our patient with a complex illness to have a normal pregnancy and delivery.
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How to cite this article: Leskovar Lemešić D, Perica D, Zlopaša G, Knezić Frković B, Šućur N, Reiner X, Pećin I. Successful pregnancy outcome in patient with Pompe disease despite discontinuation of enzyme replacement therapy. *EJCRIM* 2025;**12**:doi:10.12890/2025_005456

ABSTRACT

Background: Pompe disease (PD), is an autosomal recessive metabolic disorder caused by mutations in the acid alpha-glucosidase (GAA) gene, resulting in a deficiency of the same enzyme and glycogen buildup in tissues. Late onset PD (LOPD) is characterized by muscle illness, accompanied by diaphragmatic involvement and leading to respiratory insufficiency. Fortunately, the disease progresses slowly, and treatment with enzyme replacement therapy can further delay its development. Pregnancy in women with LOPD requires special caution because musculoskeletal changes and greater physical demands may worsen muscular weakness and endanger both the mother and unborn child. Although several cases of pregnant women with LOPD that continued enzyme replacement therapy (ERT) during pregnancy have been reported, there is still a lack of data regarding teratogenicity and safety of the foetus.

Case report: We present a case of a 31-year- old pregnant women with a mild form of LOPD who discontinued ERT during whole pregnancy. During the whole pregnancy there were no clinical signs of progression of muscle or pulmonary weakness. With careful monitoring of the patient and foetus, and planned delivery, a healthy baby girl was born. ERT was reintroduced 6 months after delivery with premedication (corticosteroids and antihistamines) for the first application, with no allergic reaction noted.

Conclusion: In this patient with well-controlled LOPD, ERT was safely discontinued during pregnancy without disease worsening. The risks of ERT in pregnancy outweighed the potential complications of well-controlled disease. The final decision should be made with an individual approach for each patient by a multidisciplinary team.

KEYWORDS

Late onset Pompe disease, pregnancy, enzyme replacement therapy, muscle weakness

EFIM
European Federation of Internal Medicine

Publisher
smc media srl

LEARNING POINTS

- Pompe disease in pregnancy represents a treatment challenge due to the increased risk of worsening respiratory and muscle function and requires a multidisciplinary approach.
- Although several case reports reported safe usage of enzyme replacement therapy (ERT) during pregnancy, more studies are needed to address the safety for the foetus and overall teratogenicity.
- In well controlled Pompe disease, ERT can be discontinued during pregnancy with careful foetal and maternal monitoring.

INTRODUCTION

Pompe disease (PD), or glycogen storage disease type II, is an autosomal recessive metabolic disorder caused by mutations in the acid alpha-glucosidase (GAA) gene, resulting in a deficiency of the same enzyme and glycogen buildup in tissues[1]. The disease has two forms: infantile onset Pompe disease (IOPD) and late-onset Pompe disease (LOPD). IOPD has more severe cardiac involvement with hypertrophic cardiomyopathy, hypotonia, and respiratory insufficiency, and is generally fatal within the first year of life if not treated. LOPD is largely a muscle illness that progresses slowly. LOPD can appear anytime from childhood to late adulthood. It has a pattern of symmetric limb-girdle muscular weakness. The weakness is accompanied by diaphragmatic involvement, leading to respiratory insufficiency early in the course of the disease. The estimate of the incidence is roughly 1/40,000 overall with around 3/4 of the cases being LOPD and 1/4 being IOPD[2]. The therapeutic options for LOPD are primarily aimed at treating the underlying enzyme deficit and managing symptoms. The mainstay of treatment is enzyme replacement therapy (ERT) with recombinant human acid alpha-glucosidase, such as alglucosidase alfa, which reduces glycogen buildup in tissues and delays disease development. Supportive therapies such as physical therapy, respiratory care, and nutritional support are critical for improving muscular function, maintaining mobility, and controlling respiratory difficulties[1,3]. Adjunctive experimental therapies, such as next-generation ERTs, chaperone therapy, and gene therapy, are being investigated to improve therapeutic efficacy and address present ERT limitations, such as the inability to pass the blood-brain barrier[3]. The combination of LOPD with pregnancy presents distinct complications for both patients and healthcare professionals. Given that most women give birth before the diagnosis, pregnancy in women with active LOPD treatment is a relatively rare and could increase disease symptoms. Pregnancy is associated with increased metabolic needs, changes in respiratory mechanics and could impact skeletal muscle function[4]. LOPD during pregnancy necessitates a multidisciplinary approach due to the unique physiological changes that can exacerbate disease symptoms. Key considerations include regular monitoring of respiratory function, since diaphragmatic weakness may deteriorate due to increased intra-abdominal pressure in later trimesters, necessitating pulmonary function testing and, if necessary, nighttime ventilator assistance. Furthermore, musculoskeletal changes and greater physical demands may worsen muscle weakness, emphasizing the need for physical therapy and mobility support. A complete delivery plan should include considerations for specialized anaesthetic methods and respiratory support during labour and postpartum recovery[4].

CASE DESCRIPTION

We present the case of a 31-year-old pregnant patient with late-onset Pompe disease, diagnosed at the age of 16. She was born from a first pregnancy complicated by maternal hypertension, but had a nor-mal birth weight, height, and Apgar score. Her neonatal and infant periods were uneventful, and psy-chomotor development proceeded normally. During her early school years, she began to experience pronounced fatigue during prolonged running and noticed she lagged behind her peers. The initial sus-picion of disease arose following elevated liver transaminase levels (aspartate transaminase, AST 114 U/l, alanine transaminase, ALT 90 U/l) and significantly increased creatine kinase (CK) levels (~1000 U/l). A thorough neurological evaluation led to a diagnosis of metabolic myopathy. Laboratory results revealed severely reduced alpha-glucosidase activity in lymphocytes. Genetic testing confirmed com-pound heterozygosity for the IVS1-13T>G mutation on one allele and the 2501delCA mutation on the other. She began ERT with alglucosidase alfa in the summer of 2010. She transitioned to adult care and had since received biweekly ERT for 14 years without complications. Annual check-ups showed no signs of disease progression. Pulmonary function tests and the 6-minute walk test remained within normal ranges. Manual muscle testing revealed only mild involvement of the trunk muscles. CK levels remained between 300–500 U/l, and myoglobin levels were <90 ng/ml.

The patient experienced no fertility issues, had no history of miscarriage, and conceived naturally while on ERT. Upon pregnancy confirmation at 9 weeks, a mutual decision was made to pause ERT and closely monitor both the patient and foetus. A multidisciplinary team, including a gynaecologist, was formed to oversee the pregnancy. Throughout the pregnancy, no foetal abnormalities were detect-ed. The patient remained clinically stable, reporting no muscle weakness or respiratory difficulties, and did not require assistive devices or respiratory support. Despite her stable condition, a caesarean sec-tion was planned at 38 weeks due to the breech position of the foetus. A healthy baby

Table 1. Published case reports of pregnant women with Pompe disease.

Reference	Age (years)	Phenotype	Symptoms during pregnancy	ERT during pregnancy	ERT restarted during pregnancy	Week of delivery	Delivery	Apgar score	Breast feeding	Complications after delivery
Weida et al., 2012[11]	23	IOPD	Worsening of motor and pulmonary function	No	No	36	C-section	9	No	DVT of upper extremity
Nampoothiri et al., 2022[12]	21	IOPD	Worsening of motor function (3rd trimester)	Yes	No	36	C-section	8	Yes	None
Houtte et al., 2019[8]	21	LOPD	Mild worsening of motor and pulmonary function	Yes	No	38	Vaginal	7	No	None
	24 (P2)	LOPD	Mild worsening of motor and pulmonary function	Yes	No	37	Vaginal	9	No	None
Santos et al., 2018[7]	32	LOPD	Worsening of motor and pulmonary function	Stopped	20 weeks of pregnancy	38	Vaginal	10	No	None
de Vries et al., 2011[9]	40	LOPD	Worsening of motor and pulmonary function	Yes	No	37	C-section	8	Yes	None
Holbeck-Brendel et al., 2017[6]	25	LOPD	Worsening of motor function (3rd trimester)	Stopped	16 weeks of pregnancy	40	Vaginal	10	No	Severe motor dysfunction, cystitis
Goker-Alpan et al., 2020[4]	> 24	LOPD	Worsening of muscle weakness	Yes	No	NA	NA	NA	NA	NA
	32	LOPD	Worsening of muscle weakness	Yes	No	NA	NA	NA	NA	NA
	36	LOPD	NA	Yes	No	NA	C-section	NA	NA	Muscle soreness and bruising
Klos et al., 2017[13]	31	LOPD	Worsening of motor and pulmonary function	Stopped	18 weeks of pregnancy	38	C-section	NA	NA	None
Koyuncu et al., 2017[14]	38	IOPD	NA	Stopped	No	38	C-section	9	Yes	None
Rohman et al. year[15]	Patient 1- P3, 29	LOPD	Worsening of muscle weakness	No	No	39	Vaginal	NA	NA	None
	Patient 1-P4	LOPD	None	Stopped	No	41	Vaginal	NA	NA	None
	Patient 2- P1	LOPD	Worsening of muscle weakness	Stopped	No	40	Vaginal	9	NA	None
	Patient 1-P5	LOPD	None	Stopped	No	42	C-section	NA	NA	None
	Patient 2-P2	LOPD	Worsening of pulmonary function	Yes	No	Elective TOP	-	-	-	-
	Patient 3-P1	LOPD	Worsening of muscle weakness	Stopped	29 weeks of pregnancy	37	C-section	9 and 10	NA	IUGR with low birthweight
	Patient 3-P2	LOPD	Worsening of motor and pulmonary function	Stopped	No	36	C-section	9 and 10	NA	None
	Patient 4	LOPD	Worsening of muscle weakness	Stopped	16 weeks of pregnancy	42	Vacuum delivery	8 and 10	NA	None
Plockinger et al., 2015[5]	38	LOPD	Worsening of muscle weakness, HELLP syndrome	Stopped	No	33	C-section	NA	NA	None
Perniconi et al., 2016[16]	28	LOPD	Worsening of pulmonary function (3rd trimester)	Yes	No	34	Vacuum delivery	10	NA	None

Abbreviations: IOPD, infantile-onset Pompe disease; LOPD, late-onset Pompe disease; P, pregnancy; ERT, enzyme replacement therapy; NA, not applicable; C-section, Caesarean section; DVT, deep vein thrombosis; IUGR, intrauterine growth restriction; TOP, termination of pregnancy.

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girl was deliv-ered, weighing 2730 grams and measuring 48 cm, with an Apgar score of 10/10. The patient recovered well from general anaesthesia and had an uncomplicated postpartum course, including successful new-born care. She chose to breastfeed for 6 months. ERT was reintroduced 6 months postpartum, with premedication (corticosteroids and antihistamines) administered before the first infusion. No allergic reactions occurred.

DISCUSSION

Studies have not demonstrated a higher rate of pregnancy, delivery, or birth complications in women with LOPD compared to the general population[5]. However, pregnancy places increased demand on the respiratory system, which may pose challenges for women with PD, particularly those with underlying respiratory muscle weakness. Additionally, adequate muscle strength is essential for labour and delivery, and progressive muscle weakness associated with PD can compromise this process. In such cases, ERT plays a crucial role in stabilizing and improving muscle function. In most reported cases of LOPD, the diagnosis of the disease was made after pregnancy, so assessing the impact of the disease on pregnancy is difficult. Unfortunately, it is well known that the symptoms of the disease themselves begin a long time before the final diagnosis is made. Goker-Alpan et al.[4] described a cohort of 25 women with LOPD, 80% of whom were diagnosed post-pregnancy. Some of them reported postpartum fatigue as one of the earliest symptoms of the disease. One patient conceived on ERT and continued treatment throughout pregnancy. The pregnancy was complicated with worsening of muscle weakness during the third trimester, which led to the recommendation to continue ERT during a subsequent pregnancy as well[4].

To date, there are fewer than 30 reports in the literature of pregnancy outcomes in women with PD *(Table 1)*. Most involve patients with LOPD who continued ERT throughout pregnancy[6-8]. These studies generally suggest that ERT is safe during pregnancy, though individual responses vary. Holbeck-Brendel et al.[6] reported the case of a 25-year-old woman with mildly symptomatic LOPD who discontinued ERT during the first trimester due to concerns about potential effects on organogenesis. The ERT was restarted again at 16 weeks and continued without complications. Despite that, at 37 weeks sudden muscle weakness and exhaustion appeared. Although caesarean section was planned, the patient spontaneously went into labour. A healthy baby was born, but the postpartum period was complicated by prolonged muscle weakness which persisted for 3 months[6]. On the other hand, most case reports describe continued ERT throughout pregnancy without clinical worsening[7,9]. De Vries et al.[9] addressed concerns about the safety of breastfeeding while on ERT. By measuring the concentration of alglucosidase alpha in the breast milk they concluded that 24 hours after ERT there is no enzyme activity in breast milk, indicating that breastfeeding during ERT is safe[9]. The European Reference Network for Metabolic Diseases recommends continuation of ERT during pregnancy as there are several reports on safe usage and the absence of embryo-foetal toxicity in animal studies[10]. It also reports that cessation of ERT during pregnancy may result with an increased risk of allergic reaction upon reintroduction[10]. However, more studies are needed to address safety for the foetus and potential teratogenicity of ERT during pregnancy.

CONCLUSION

Although the guidelines, based on several case reports, advise the continuation of ERT in the pregnant women with PD, given the still insufficient evidence, it is necessary to make the decision on a case-by-case basis. Our case report of a pregnant woman with mild clinical manifestations of LOPD demonstrates how ERT could be temporary discontinued with close monitoring of both mother and foetus, without clinical deterioration. It is important to emphasize that in this particular case, the potential risks associated with ERT were considered to outweigh the risks posed by a well-controlled form of the disease.

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