PRACE KAZUISTYCZNE
położnictwo

Pregnancy, delivery and puerperium in a patient with lysinuric protein intolerance – a case report

Ciąża, poród i połóg u pacjentki z lizynuryczną nietolerancją białka – opis przypadku

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Abstract

The paper presents the course of pregnancy, delivery and early postpartum period in a 23-year-old woman with lysinuric protein intolerance (LPI). The pregnancy was uneventful and resulted in a caesarean birth to a healthy baby at 37 weeks gestation. Nevertheless, the course of pregnancy in women with LPI is associated with a significantly increased risk of serious complications, including acute hyperammonemia, preeclampsia and postpartum bleeding, as well as fetus intrauterine growth retardation.

In many cases, intensive metabolic monitoring and a proper diet with protein limitation and appropriate amino acids supplementation may significantly reduce the risk for both the mother and the newborn.

Key words: **lysinuric protein intolerance** / **pregnancy** / **hyperammonemia** /

Streszczenie

W pracy przedstawiono przebieg ciąży, porodu i wczesnego okresu połogu u 23-letniej pacjentki z lizynuryczną nietolerancją białka. W opisanym przypadku ciąża przebiegła bez istotniejszych powikłań i zakończyła się urodzeniem drogą cięcia cesarskiego zdrowego dziecka w 37. tygodniu ciąży. Przebieg ciąży u kobiety z tą chorobą metaboliczną wiąże się z podwyższonym ryzykiem wystąpienia poważnych powikłań, w tym stanu przedrzucawkowego oraz krwawienia poporodowego, a także ograniczenia wewnątrzmacicznego wzrastania płodu.

Intensywny nadzór metaboliczny oraz prawidłowa dieta z ograniczoną podażą białka i suplementacją odpowiednimi aminokwasami w wielu przypadkach pozwala zdecydowanie zmniejszyć ryzyko zarówno dla matki jak i dla noworodka.

Słowa kluczowe: **lizynuryczna nietolerancja białka** / **ciąża** / **hiperamonemia** /

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Introduction

Nowadays, with early diagnosis and effective medical care, an increasing number of women with inborn errors of metabolism (IEM) are now reaching adulthood and child-bearing age. Because of the rarity of most of IEM, the knowledge about risks factors associated with pregnancy remains limited. Pregnancy-related problems in these patients are either connected with the effects of pregnancy on the maternal metabolic disorders or the relation between the mother and the fetus, depending on whether the former or the latter is affected. For certain metabolic disorders, including different types of hyperamonemias, maternal risk associated with pregnancy can be considerably high [1].

Lysinuric protein intolerance (LPI; OMIM 222700) is an autosomal recessive disease associated with a basolateral transport defect of dibasic amino acids in epithelial cells of the renal tubule and the small intestine. The disease occurs most frequently in the Finnish and Italian populations. The reduced activity of the transporter (SLC7A7) leads to a reduced absorption of arginine, ornithine, and lysine in the intestine and to an increased loss of the amino acids by the kidneys. It results in lower concentrations of dibasic amino acids in the serum. Arginine, ornithine and lysine, in appropriate amounts, are necessary for the proper function of the urea cycle - the primary route of ammonia detoxification. The cycle disorders lead to hyperammonemia with all its consequences [2, 3, 4, 5].

LPI is a metabolic disease whose signs and symptoms may differ significantly in individual patients. They are also dependent on the age of the patient. The absence of symptoms is typical for breast-feed infants, but severe complications, sometimes life-threatening, may occur after weaning, in adolescence and adulthood, mainly after high-protein intake [2, 4, 5, 6].

Major signs of acute metabolic decompensation are nausea, vomiting and gradually increasing unconsciousness. Chronic symptoms include recurrent vomiting with episodes of diarrhea, poor feeding, aversion to protein-rich food, failure to thrive, episodes of somnolence and coma. Additionally, hepatosplenomegaly, poor growth, early osteoporosis (often severe), pulmonary involvement, renal involvement, and macrophagic activation syndrome may occur [2, 4, 5, 7].

The diagnosis of LPI is established by the finding of increased amino acid excretion in the urine (mainly lysine) and a high level of ammonia in the blood, especially after protein meal.

Other typical deviations in laboratory studies include: orotic aciduria, mild normochromic anemia with anisocytosis and poikilocytosis, thrombocytopenia, elevated ferritin, lactate dehydrogenase, glutamine and glutamic acid. Decreased concentration of cationic amino acids (Lys, Arg, Orn) in serum is also typical [2, 4, 5, 7].

Protein intake reduction followed by citrulline supplementation are the key elements of proper treatment. Citrulline is an intermediate in the urea cycle, but also a precursor of arginine and ornithine. It requires a transporter for neutral amino acids (not for basic amino acids), thus it can be absorbed properly in patients with LPI and adequately support the detoxification pathway of ammonia [2, 5].

During pregnancy and delivery many metabolic processes intensify due to significant hormonal changes in the body of the mother. It is mainly emphasized in protein catabolism, which increases the risk of metabolic decompensation in patients with LPI. It may compromise the health and even the life of the pregnant or puerperal women. Due to dietary restrictions, associated anemia or thrombocytopenia, the risk of complications for the mother and the fetus may indeed be great [1, 2, 5, 6, 7, 8].

The aim of our report was to present the course of pregnancy, culminating in the birth of a healthy newborn, and the postpartum period in a woman with lysinuric protein intolerance.

Case report

The patient was a 23-year-old pregnant woman with a history of one miscarriage and the metabolic disease - lysinuric protein intolerance diagnosed at the age of 17. The anamnesis findings revealed appendectomy, surgical correction of strabismus, amblyopia, and congenital cataract of the left eye and hyperopia. The patient remained under routine medical care of Metabolic Diseases Department of The Children's Memorial Health Institute in Warsaw.

Biochemical signs of increasing metabolic decompensation had been presenting since her check-up at 17 weeks gestation onwards. Due to this reason, at 29 weeks gestation she was admitted to the Department of Endocrinology, Metabolic Diseases and Internal Medicine, Pomeranian Medical University. On admission the patient did not report any discomfort. The physical examination revealed a slightly enlarged liver, reaching 2 cm below the costal arch at the right midclavicular line, with a sharp edge, with no tenderness. Laboratory tests showed a normocytic anemia, thrombocytopenia, low magnesium and PTH concentrations with normal values of calcium and phosphate. In addition, a high level of lactate dehydrogenase and ferritin (abnormalities characteristic of patients with LPI), as well as low levels of vitamin B12, mild hypoproteinemia and hypoalbuminemia were found. Vitamin B12 and L-arginine supplementation was prescribed. Due to severe anemia, red blood cells were transfused. Generalized urticaria and irregularities in CTG appeared as the transfusion complications. The patient received 100 mg of hydrocortisone intravenously and was transferred to the Department of Obstetrics and Gynecology, Pomeranian Medical University, where ultrasound examination and CTG were performed to assess fetal well-being. The condition of the child was good. Systemic prednisone therapy was implemented (30 mg, orally, every second day) due to increasing thrombocytopenia (platelet count nadir 57.9 G/L). Since the risk of preterm delivery resulting from possible complications of LPI appeared to be very high, the patient received betamethasone 12 mg daily i.m. for two consecutive days to accelerate fetal lung maturation. Vitamin B12 and L-arginine were continued.

The patient was discharged at 30 weeks gestation in a stable condition and well-compensated metabolic state (normal serum concentration of ammonia). Her ammonia levels were monitored systematically. Vitamin B12 and L-arginine supplementation was continued along with a low-protein diet (the natural protein 1g/per kg/per day).

During the visit at 31 weeks gestation, ammonia concentration in blood serum was assessed (160 ug/dl; normal range: 19-87 ug/dl), good fetal condition as well as stable maternal state were confirmed. The continuation of the therapy was recommended.

At 33 weeks gestation, the patient was admitted to the hospital once again due to abdominal pain, to assess the risk of preterm delivery. Laboratory tests revealed normocytic

anemia, a decreased number of platelets and high concentration of ammonia (320 ug/dl). The patient did not comply with the prescribed low-protein diet. Amino acids serum concentration revealed low concentrations of tyrosine, valine, isoleucine, leucine, phenylalanine, ornithine, and lysine but an increased concentration of alanine. Other amino acids concentrations remained stable and within normal limits. Serum orotic acid concentration was within the normal range. CTG and ultrasound examinations revealed that the condition of the fetus was good. The risk of preterm delivery was not confirmed.

Significant restriction in protein intake was implemented – initially up to 0.5 g/per kg/per day, then up to 1.0 g/per kg/per day. The patient also received intravenous infusions of 10% glucose (20 ml/hour) throughout the day, Dialamine 20g per day (in four equal doses), L-arginine at a dose of 3x2 g and L-citrulline at a dose of 3x10g. Prednisone was continued. All the symptoms vanished within a few days. Ammonia concentration also normalized within 3 days.

At 37 weeks gestation, the patient gave birth to a healthy girl (weight 2430 g), by a cesarean section necessitated by a premature rupture of membranes as well as the metabolic disease. In the early postpartum period an intensive metabolic monitoring was continued (concentration of ammonia remained within the range of 19.2 ug/dl-106.3 ug/dl), along with the restriction in protein intake with the gradual increase from 0.5 to 0.8 g/kg/day, L-arginine supplementation at a dose of 3x2g, L-citrulline (3x10g) and Dialamine (4x10g). Prednisone was discontinued gradually.

The post-operative wound healing process was uneventful. The surgical suture was removed on the eighth and the patient was discharged on the ninth postpartum day in good overall condition, with no signs of metabolic decompensation. The newborn left the hospital also in a very good condition. Low-protein diet along with Dialamine, L-arginine and L-citrulline supplementation was recommended for the patient. She was also advised to visit the Metabolic Disorders Outpatient Clinic at The Children's Memorial Health Institute in Warsaw.

Discussion

Pregnancy in patients with LPI is associated with an increased risk of complications for both the mother and the fetus. Tanner et al., present the course of 19 pregnancies in 9 Finnish women. The most common complications during pregnancy in those cases were toxemia (8 patients) and anemia (6 patients). The most frequent perinatal complication was abnormal bleeding associated with thrombocytopenia (4 cases). The authors also report a high risk of hypertension and renal complications arising during the pregnancy. In their study, they describe a case of a hypertensive crisis, which was the indication for delivery by means of a cesarean section at 30 weeks gestation [2].

Simell presented a course of 7 pregnancies in 4 patients with LPI. The most common complications during pregnancy in his report were thrombocytopenia and anemia, which occurred in all women. In addition, he reported one case of bleeding as a complication of amniocentesis (also described by Tanner et al.), one case of toxemia and eclampsia and two deliveries in one patient complicated by a pathologic bleeding. Only one patient had two uneventful pregnancies [9].

Takayama et al., described one case of a pregnancy complicated by thrombocytopenia, anemia, and hyperammonemia, resulting in a spontaneous vaginal delivery of a healthy boy at 37 weeks gestation [7].

Similarly to the abovementioned authors, we also observed thrombocytopenia and anemia requiring red blood cell transfusion. Anemia and thrombocytopenia (as well as leukopenia) are common hematological symptoms in patients with LPI, also beyond pregnancy.

In case of our patient, we found a significant increase in the levels of ammonia resulting from her dietary non-compliance. The highest risk of metabolic decompensation in pregnant women is associated with the delivery and puerperium due to intensified catabolism. Toxemia may develop rapidly and culminate in convulsions, cerebral hemorrhage, disseminated intravascular coagulopathy, pulmonary edema, renal failure, liver hemorrhage, including hyperammonemic encephalopathy and death [2,6,8].

All the above cited authors agree that pregnancy in a patient with lysinuric protein intolerance presents is a complex clinical challenge, mainly because of the rarity of the disease. Moreover, the underlying disease increases the risk of pregnancy complications and, simultaneously, the pregnancy increases the risk of metabolic decompensation. However, reports indicate that intensive biochemical monitoring, proper diet with limited protein intake and appropriate amino acids supplementation may minimize the risk of complications and lead to a successful delivery of a healthy child.

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