

WILSON'S DISEASE IN PREGNANCY

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SUMMARY – Wilson's disease is a rare autosomal recessive disorder of copper metabolism. It causes cirrhosis of the liver, consequently followed by disorder of the menstrual cycle and infertility. Successful decopperizing may lead to restoration of the ovulatory cycle and enable pregnancy. Increased copper levels may cause preeclampsia, intrauterine growth restriction and neurologic damages in the fetus. Pregnant women with decompensated liver cirrhosis face more complications, including bleeding from esophageal varices, liver failure, encephalopathy, and rupture of the splenic artery. We present a case of Wilson's disease in a patient who had spontaneously conceived three times. The first pregnancy ended with delivery of a healthy baby at term. In second pregnancy, medically induced abortion was performed in the 12th week because of deterioration of the underlying disease, liver cirrhosis with portal hypertension. In the same year, the patient underwent liver transplantation. Two years after the transplantation, the patient spontaneously conceived and delivered vaginally a healthy child.

Key words: Hepatolenticular degeneration; Liver cirrhosis; Pregnancy; Case report

Introduction

Wilson's disease is a rare autosomal recessive disorder accompanied by disturbed copper metabolism. The dominant pathophysiological mechanism is copper accumulation in certain organs, primarily in the liver and brain. The incidence ranges from 1:30 000 to 1:100 000. Kinnier Wilson was the first to describe the disease in 1912¹. The disorder is most commonly manifested in the early twenties. Without appropriate treatment, the chance for a successful pregnancy is notably decreased due to the impaired fertility caused by liver insufficiency². Disturbed copper metabolism may be associated with preeclampsia and intrauterine growth restriction³. Successful pregnancy is rare in patients with liver cirrhosis. The incidence of such pregnancies is unknown, since cirrhosis rarely affects

women in their reproductive age. It is estimated to 45 cases *per* 100 000 women of reproductive age. Cirrhosis of the liver results in hormonal and metabolic disorders, which may cause anovulatory cycles and amenorrhea⁴.

Case Report

The patient was born in 1976. She was diagnosed with the hepatic type of Wilson's disease in 1991. Since 1991, she had been on continuous therapy with d-penicillamine. In 2001, the patient conceived spontaneously for the first time. She delivered vaginally at term a healthy male child, 3050 g/52 cm. During and after the pregnancy, the patient had been treated with d-penicillamine. In 2003, the patient conceived spontaneously for the second time. The pregnancy was terminated in the 12th week because of portal hypertension. Due to the advanced cirrhosis of the liver, the patient underwent liver transplantation in the same year. In 2005, two years after the transplantation, the

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patient conceived spontaneously again. The pregnancy was uneventful. The results of all biochemical tests during pregnancy were normal, except for platelet count ranging from 49 to $85 \times 10^9/L$. Thrombocytopenia was also present before pregnancy, probably as a consequence of spleen enlargement. Abdominal ultrasonography showed normal blood flow through the portal vein and other hepatic vessels, and an enlarged spleen, 180x160 mm in size, with a venous convolute in the hilus. Ultrasound of the fetus was normal, with fetal growth and development appropriate for gestational age. She gave birth to a healthy male child, 4110 g/52 cm, in the 40th week of pregnancy.

Discussion

Wilson's disease affects people all over the world, regardless of their sex, race or nationality¹. The ATP7B gene, which is responsible for the occurrence of Wilson's disease was discovered in 1993. It is located on the 13th chromosome. It codes the enzyme type P adenosine triphosphate, which is expressed mostly in hepatocytes. The enzyme is responsible for the transmembrane transport of copper in hepatocytes. The accumulation of copper in the liver is the result of a decreased hepatocellular excretion of copper to the gallbladder caused by the lacking or decreased function of ATP7B protein. There is over one hundred mutations of this gene, which may trigger the occurrence of Wilson's disease⁵. Both parents must be carriers of the pathological gene for Wilson's disease to be inherited. If both parents carry the gene for Wilson's disease, the probability for the child to develop Wilson's disease is 25%¹.

When the capacity for storing copper in the liver is exceeded, copper appears in the bloodstream. Consequently, it accumulates in other organs, most notably the brain, the kidneys and the cornea. The decreased function of ATP7B protein causes yet another problem. It is a disorder of copper implantation in the ceruloplasmin, a protein that binds copper. Most of the copper from food becomes absorbed in the duodenum and proximal part of the small intestine. It binds to albumin and is transported to the liver through portal bloodstream. In the circulation system, 90% of copper binds to ceruloplasmin. In the states of hyperestrogenism, such as pregnancy, the concentration of

ceruloplasmin is decreased⁶. Exceeded accumulation of copper primarily damages the liver and the brain, which results in development of liver diseases (45%-58%), neuropsychiatric diseases (30%-33%), or both. The symptoms of Wilson's disease most commonly appear in adolescence or in the twenties². Our patient had experienced the first symptoms while an adolescent. Before the first symptoms appear, there is a period without any symptoms during which copper gets accumulated in the body. The manifested liver disease may range from unspecific hepatomegaly to serious cases of liver cirrhosis and acute liver failure⁷. Isolated splenomegaly due to the cirrhosis of the liver caused by portal hypertension may be perceived as one of the first symptoms⁶. The majority of patients with Wilson's disease develop liver cirrhosis⁶.

About 40%-50% of patients with Wilson's disease suffer from neuropsychiatric symptoms⁷. They can develop hepatic encephalopathy. Hepatic encephalopathy is characterized by a wide spectrum of neuropsychological disturbances, ranging from sleep disorders, changes in personality, degradation of cognitive functions, and of neural and motor functions⁸. Indicative of Wilson's disease is the Kayser-Fleischer ring appearing on the cornea. It is a result of copper accumulation in the cornea and is reported in 60% of Wilson's disease patients⁷. The Kayser-Fleischer ring affects 95% of patients suffering from neuropsychiatric symptoms⁷.

Compensated liver cirrhosis without portal hypertension is not a contraindication for pregnancy⁵. Portal hypertension increases the risk of complications for mothers⁵. The most important complications include bleeding from esophageal varices, which affects 18%-32% of pregnant women with Wilson's disease and 50% of pregnant women with portal hypertension. Bleeding from esophageal varices is associated with a mortality rate of 50%. About 24% of pregnant women develop decompensation of liver disease, ascites and portal encephalopathy. Pregnant women with liver cirrhosis have a higher risk of the splenic artery rupture (2.6%) with consequent hypovolemic shock. Maternal mortality rate in such cases is extremely high and is reported to be 70%. In comparison to the general population, decompensated liver cirrhosis increases the incidence of spontaneous abortion (30%-40% as opposed to 15%-20%) and premature labor (25%)⁴.

Due to liver cirrhosis with portal hypertension, our patient's second pregnancy was terminated by a medically induced abortion in the 12th week of gestation.

Only a few successful pregnancies in women with Wilson's disease have been described. Chronic liver disease and toxicity of copper disturb menstrual cycle. Major problems are infertility and recurrent spontaneous abortions². Recurrent spontaneous abortions are common in the first trimester. They are considered to be the consequence of accumulated copper in the uterus, especially when the patients have not been medically treated³. Sinha *et al.* demonstrated an increased prevalence of spontaneous abortions in untreated pregnant women with Wilson's disease when compared with the treated ones⁹. Treated patients have a high probability of conceiving a child².

The increased copper levels may be related to the development of preeclampsia caused by copper accumulation in the liver. It may also cause intrauterine growth restriction. The fetus may also suffer neurologic damages, which are often a result of hypoxia caused by the accumulation of copper in the placenta and fetal tissue³.

Once diagnosed, Wilson's disease has to be treated for life. The accumulated copper must be removed using chelating agents. Therapy consists of four medications: d-penicillamine, trientine, zinc salts and ammonium tetrathiomolybdate, which are classified as Pregnancy Category C drugs by the Food and Drug Administration⁴.

The medications used for the treatment of Wilson's disease are not contraindicated in pregnancy. Therapy most commonly used in pregnancy is d-penicillamine. It mobilizes tissue copper and increases its excretion by urine. It has been used since 1965. Numerous side effects of d-penicillamine have been reported in 30% of cases⁶. Side effects that occur within three weeks of commencing medication include lymphadenopathy, neutropenia and proteinuria, which can later be followed by nephrotoxicity, a syndrome resembling lupus with hematuria, aplastic anemia and skin rash⁶. In the initial stage of treatment with d-penicillamine, neurologic symptoms deteriorate in 10%-20% of cases⁶.

Although considered to be a safe choice in pregnancy, in a small number of cases d-penicillamine has been reported to cause congenital malformations of the fetus, including fragile blood vessels, low positioned

ears, micrognathia, and hyperflexy hips and joints³. Our patient had been treated with d-penicillamine and gave birth to a healthy child. The second most commonly used medication is zinc salt, which has been used since 1960. There are reportedly less side effects than with d-penicillamine therapy, with no deterioration of neurologic symptoms. Zinc salt is as effective as d-penicillamine and patients tolerate it better. Trientine has been used since 1969. It is similar to d-penicillamine, but has a less potent effect. Ammonium tetrathiomolybdate is a strong chelating agent. It does not cause deterioration of neurologic symptoms⁶. Cessation of the drug treatment may cause an acute liver failure⁶. In comparison to the dose of chelating agents (d-penicillamine and trientine) taken before pregnancy, the dose should be reduced by 25%-50% during pregnancy. It is of utmost importance in the third trimester if cesarean section is to be performed. A lower dose of chelating agents speeds up the healing process. There is no need to reduce the dose of zinc salts⁶. Liver transplantation is the first-line therapy for patients with fulminating disease and those suffering from decompensated liver cirrhosis. Clinical manifestations may improve during pregnancy due to the increased copper need of the fetus and quadruple ceruloplasmin level in pregnant women¹⁰.

Our patient had spontaneously conceived and gave birth to a healthy male child ten years after being diagnosed with the hepatic type of Wilson's disease. The patient had been treated with d-penicillamine. The patient's second spontaneous pregnancy was terminated in the 12th week by a medically induced abortion due to deterioration of liver cirrhosis with portal hypertension. In the same year, the patient underwent liver transplantation. Two years after the transplantation, the patient spontaneously conceived and gave at term birth to a healthy child.

Conclusion

Wilson's disease is a rare congenital disease. Spontaneous abortions are common in untreated patients. Treated patients have a high probability of getting pregnant and giving birth to a child. Pregnant women with decompensated cirrhosis of the liver are at a greater risk of developing complications during pregnancy. Liver transplantation is the first-line therapeutic

tic option for patients suffering from decompensated liver disease. These pregnancies demand intense monitoring and team work in order to achieve a successful outcome for both the mother and the child.

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Sažetak

WILSONOVA BOLEST U TRUDNOĆI

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Wilsonova bolest je rijedak autosomno recesivni poremećaj metabolizma bakra. Uzrokuje cirozu jetre te posljedično poremećaj menstrualnog ciklusa i infertilitet. Uspješna dekuprinizacija može dovesti do ponovne pojave ovulacijskih ciklusa i omogućiti trudnoću. Povećane vrijednosti bakra mogu uzrokovati preeklampsiju, intrauterini zastoj u rastu te neurološka oštećenja ploda. Trudnoća kod trudnica s dekompenziranom cirozom jetre povećava komplikacije kod majke, uključujući krvarenje iz varikoziteta jednjaka, zatajenje jetre, encefalopatije i rupturu lijenalne arterije. Prikazuje se bolesnica s Wilsonovom bolešću koja je tri puta spontano zaniijela. Prva trudnoća okončana je porodom zdravog djeteta u terminu. Druga trudnoća prekinuta je u 12. tjednu medicinski induciranim pobačajem zbog pogoršanja osnovne bolesti, ciroze jetre s portalnom hipertenzijom. Iste godine u bolesnice je učinjena transplantacija jetre, a dvije godine nakon transplantacije spontano je zaniijela i vaginalno rodila zdravo dijete.

Ključne riječi: *Hepatolentikularna degeneracija; Trudnoća; Jetrena ciroza; Prikaz slučaja*