International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Devraj NT et al. Int J Reprod Contracept Obstet Gynecol. 2025 Oct;14(10):3552-3555
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20252890

Case Report

Pregnancy with Wilson's disease

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Received: 15 August 2025
Revised: 30 August 2025
Accepted: 01 September 2025

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ABSTRACT

Wilson's disease is a rare, autosomal recessive disorder characterized by impaired liver metabolism of copper, leading to decreased biliary excretion and incorporation of ceruloplasmin levels mainly in the liver and brain. Untreated Wilson's disease has been shown to cause subfertility and miscarriages. Pregnancy management in women with Wilson's disease remains an important clinical problem. Early recognition and effective management can help prevent the disease progression and hence give eventful progress and perinatal outcomes. We hereby report the case of a 29-year-old pregnant multigravida with known case of Wilson's disease since childhood, and on treatment with copper chelating agents and zinc sulphate. She was followed up from early pregnancy till delivery at our hospital. She was monitored in combined obstetric, medicine and neurology clinic. Her pregnancy and postpartum course remained uneventful. She had a spontaneous vaginal delivery at 38+5 weeks period of gestation and gave birth to healthy female baby of 2.66 kg in weight. The infant was genetically screened and was found to be carrier free. It is relatively safe for women with Wilsons disease to become pregnant. Patients with Wilson's disease receiving regular treatment who remain asymptomatic are usually able to conceive and achieve successful outcomes. However, these pregnancies should be considered as high risk and merit regular surveillance.

Keywords: Copper, Miscarriages, Copper chelating agent, Zinc sulphate, Wilsons disease

INTRODUCTION

Wilson disease is a rare autosomal recessive disorder of copper homeostasis affecting 1:50 to 1:100,000 individuals.[1] It is characterized by excess copper deposition due to a mutation in ATP7B gene on chromosome 13q14. which lead to impaired biliary excretion and ceruloplasmin incorporation causing copper accumulation in the liver and brain resulting in liver cirrhosis and nervous system manifestations.[2] Untreated Wilson disease results in oligomenorrhea, subfertility, and spontaneous miscarriage. This is due to hepatic dysfunction causing reversible hormonal changes. Free intrauterine copper derived from non-ceruloplasmin-bound copper is excess in such patients. Also, diffusion of non-ceruloplasmin-bound copper from plasma into tissues may affect ovarian follicular aromatase activity.[3] Patients with Wilson disease who receive regular treatment and who remain asymptomatic usually conceive normally and have favourable pregnancy outcomes.

CASE REPORT

A 29-year-old multigravida, booked case, followed up in our antenatal clinic from early pregnancy till delivery. She is a known case of Wilson's Disease since childhood, on treatment with D-penicillamine 250 mg. She was completely symptom free when she presented to our hospital.

History of present pregnancy

The present pregnancy was spontaneously conceived. After confirmation of pregnancy, she was followed up in

our hospital since, 10 weeks period of gestation. She was asymptomatic and on examination was found to have Kayser Fleischer ring and fine tremors. There were no signs of jaundice, hepatosplenomegaly or ascites. Neurologist opinion was sought and advised assessment of serum copper and ceruloplasmin levels which were found to be normal. She was advised to increase dose of D-penicillamine 250 mg to 500 mg with zinc sulphate 220 mg. After 2 weeks she was followed up with NT/NB scan which showed normal NT and raised peripheral resistivity index with early diastolic notching in bilateral uterine arteries. Hence Tablet Ecosprin 150 mg was started prophylactically. TIFA scan done at 22 weeks was found to be normal. She was compliant with medication and showed adequate growth with normal liquor in the interval growth scan.

Past history

The patient was diagnosed with Wilson's disease when she presented with jaundice and ascites. After workup, she was diagnosed with Wilson's disease and started with D-penicillamine and zinc sulphate, she was compliant to the medications till the age of 15 years. After that, she abruptly stopped the medications. During her first pregnancy, she had neuropsychiatric symptoms in first trimester such as tremors, slurred speech, and gait abnormality. For further management, she was referred to a higher neurology centre where she was started on oral D-penicillamine and zinc sulphate throughout pregnancy. First pregnancy was uneventful. She continued the tablets for 2 months after the delivery and stopped thereafter. The first baby is currently healthy and has been screened for Wilson's disease.

Family history

She had three siblings who were known case of Wilson's disease and they died at the age of around 10-15 years. Nephew is also a known case of Wilson's disease.

Delivery history

She had a full-term vaginal delivery at 38+5 weeks of gestation with a spontaneous onset of labor. She delivered a female baby of 2.66 kg, with a good APGAR score. There were no labor complications noted. Postpartum period was uneventful. Baby was screened for Wilson's disease and found to be carrier free.

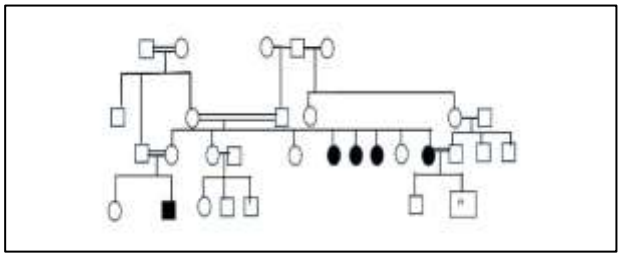

Figure 1: Pedigree chart of the family.

DISCUSSION

In 1912, Dr. Samuel Kinnier Wilson first described Wilson's Disease an autosomal recessive disorder.[4] The incidence in obstetric population is 1 per 50,000 to 1,00,000.[5] Liver is the primary storage organ for copper from which it is distributed in circulation to other tissues such as nervous system, eyes and kidneys.[6] The ATP7B gene, which is responsible for the occurrence of Wilson's disease was discovered in 1993.[7] It is located on the 13th chromosome. It codes the enzyme type P adenosine triphosphate. The enzyme is responsible for the transmembrane transport of copper in hepatocytes. There are over one hundred mutations of this gene, which may trigger the occurrence of Wilson's disease.[8] If both parents carry the gene for Wilson's disease, the probability for the child to develop Wilson's disease is 25%.[9] The decreased function of ATP7B protein causes a disorder of copper implantation in the ceruloplasmin, a protein that binds copper.

Copper from food becomes absorbed in the duodenum. It binds to albumin and is transported to the liver through portal bloodstream.[10] 90% of absorbed copper binds to ceruloplasmin. In the states of hyperestrogenism, such as pregnancy, the concentration of ceruloplasmin is decreased. 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.[11] The symptoms of Wilson's disease most commonly appear in adolescence or in the twenties. The manifested liver disease may range from unspecific hepatomegaly to serious cases of liver cirrhosis and acute liver failure.[12] About 40%-50% of patients with Wilson's disease suffer from neuropsychiatric symptoms like hepatic encephalopathy which 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 functions (dyskinesis and tremors).

Kayser-Fleischer ring appearing on the cornea is a result of copper accumulation in the cornea and is reported in 60% of the patients.[13] Compensated liver cirrhosis without portal hypertension is not a contraindication for pregnancy. Portal hypertension increases the risk of complications for mothers. The most important complications include bleeding from esophageal varices, which affects 18-32% of pregnant women with Wilson's disease.[14] 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.

In comparison to the general population, decompensated liver cirrhosis increases the incidence of spontaneous abortion (30%-40%) and premature labor (25%).[15] Chronic liver disease and toxicity of copper causes menstrual disturbances, infertility and recurrent first trimester abortions. The increased copper levels may be

related to the development of preeclampsia and fetal 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 tissue. The serum copper levels may increase till 24 weeks followed by a modest decline probably due to fetal intake of copper. There is approximately 12 mg of copper in a neonate and the fetus removes an average of 0.044 mg of copper per day from the maternal blood, due to which improvement in symptoms of Wilson's disease have also been reported.[16] The prognosis of Wilson's disease is predicted by Nazer's prognostic index based on serum bilirubin, serum aspartate aminotransferase levels and prothrombin time.[17]

Score <7 medical therapy. Score >9 considered for liver transplantation. For patients with scores between 7 and 9 clinical judgements.

In 1951 the first chelating agent was introduced for the treatment of Wilson's Disease-British anti-lewisite. In 1956, D-penicillamine discovered by John Walsh revolutionized treatment of this disorder.[18] Other treatment modalities include zinc salts to block enteral copper absorption, tetra thiomolybdate (TM) to chelate copper and block enteral absorption, and orthotropic liver transplantation. These drugs are classified as pregnancy category C by the FDA.[19]

Penicillamine produces adverse effects like skin rash, fever, eosinophilia, thrombocytopenia, leukopenia, and lymphadenopathy in 20-30% patients. The dose of penicillamine should be reduced to 250 mg/day, 1 to 6 weeks prior to caesarean delivery, to prevent delayed wound healing. There have been some congenital malformations reported with use of D-penicillamine including collagen vascular disease, low-set ears, and micrognathia. Zinc is increasingly being used as a therapeutic option in managing Wilson's disease nowadays. Zinc interferes with the absorption of copper from the gastrointestinal tract; however, its long-term side-effects are still not well studied.

Management involves regular physical examination especially ophthalmologic exam. Serum copper and ceruloplasmin levels, liver biochemistries, complete blood count, coagulation profile and urinalysis should be done at least twice annually. They should also have 24-hour urinary excretion of copper measured yearly. Treatment is lifelong and can only be discontinued if a liver transplant has been performed.[20] Pregnant women with Wilson's Disease should be managed in multidisciplinary center. Pregnancy does not have any effect on the disease process.[21] Baby should be genetically screened especially if the father is carrier as in that case will have 50% risk of having an affected child.[22]

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 healthy child. In families with history of Wilson's disease, screening of all members may allow early detection of carriers and affected individuals. Thus, early initiation of treatment in childhood before the onset of symptoms may allow a normal length & quality of life. It can be fatal or disabling, if left untreated. Hence, need of lifelong treatment should be stressed. In well treated Wilson's disease, pregnancy does not appear to be contraindicated and does not have an effect on the progression of disease. Premarital screening of the spouse to rule out carrier state can help prevent further cases of Wilson's disease.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Devraj NT, Ramalingappa P, Shukla A. Pregnancy with Wilson's disease Int J Reprod Contracept Obstet Gynecol 2025;14:3552-5.