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Pregnancy With Wilson's Disease

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To editor:

Wilson's disease (WD) is a metabolic genetic disorder characterized by the copper accumulation, leading to toxic damage, particularly in the liver and nervous system. Initially described by Kinnier Wilson in 1912,[1] WD is caused by mutations in the ATP7B gene, located on the long arm of chromosome 13, resulting in the absence or dysfunction of ATPase, a protein essential for regulating copper levels in the body. The prevalence of WD is estimated at 1 in 30,000 individuals, with a carrier frequency of 1 in 150–180. Clinically, female patients with WD often experience irregular menstruation, amenorrhea, and ovulation failure, contributing to reduced fertility, spontaneous miscarriage, and infertility. However, successful pregnancies in WD patients are documented. Several anti-copper agents have been approved and are associated with favorable pregnancy outcomes in these cases. This correspondence presents a case of a successful pregnancy in a woman with WD, alongside a comprehensive review of relevant literature on the topic.

Case presentation

A 26-year-old patient, gravida 8 para 2, was diagnosed with Wilson's disease in 2016, presenting with hepatic, neurological, and psychiatric symptoms. A slit lamp examination revealed Kayser-Fleischer rings in the cornea, and ultrasonography confirmed liver cirrhosis. Due to irregular drug therapy, her condition deteriorated in 2017. This resulted in liver damage, an enlarged spleen, ascites, low platelet count, and anemia. To manage her condition, she was subsequently treated with oral D-penicillamine or meso-2,3-dimercaptosuccinic acid, which effectively stabilized her condition for 3 years.

Since her diagnosis, the patient has experienced seven pregnancies. Her obstetric history includes four spontaneous miscarriages, two full-term births, and two elective terminated pregnancies in the first trimester. Prior to her WD diagnosis, she had one pregnancy terminated at 8 weeks of gestation for personal reasons. A timeline of the patient's pregnancies and treatments is provided in Figure 1.

One year after diagnosis, the patient achieved a spontaneous vaginal delivery of a healthy male infant weighing 3400 grams at full term without requiring medical intervention. In June 2019, she became pregnant again and discontinued penicillamine therapy during the first trimester. Initial laboratory results during this pregnancy indicated a hemoglobin level of 107 g/dl, white blood cell count of 4.2×10^3 µl, platelet count of 92×10^3 µl, and blood albumin level of 38.1 g/L. Thyroid, hepatic, renal, coagulation, and lipid functions were within normal limits. The pregnogram and fundal height growth remained within the expected range. Throughout her pregnancy, the patient's hemoglobin levels fluctuated between 98 and 107 g/dl, her platelet count ranged from 89×10^3 to 129×10^3 µl, with stable hepatic, renal, coagulation functions, and blood pressure. At 39+5 weeks of gestation, she delivered a healthy female infant weighing 2900 grams via spontaneous vaginal delivery. The newborn's Apgar scores were 9 and 10 in 1 and 5 minutes, respectively. Both mother and newborn were discharged 24 hours postpartum. Postpartum blood tests revealed a hemoglobin level of 113 g/dl, white blood cell count of 11.34×10^3 µl, and platelet count of 144×10^3 µl.

Unfortunately, spontaneous miscarriages occurred in 2016, 2018, 2020, and 2023, all following her diagnosis. In October 2020, she experienced a spontaneous miscarriage at 10 weeks of gestation while on a maintenance dose of D-penicillamine (1125 mg/day). Embryonic chromosome DNA analysis revealed a normal karyotype (46XX); however, serum copper and ceruloplasmin levels were elevated (37.24 ug/dl and 0.0382 g/L, respectively).

At the most recent follow-up, the patient remained on a maintenance dose of D-penicillamine (1125 mg/d), with hepatic function, renal function, coagulation parameters, and psychosis status. In October 2023, she had unplanned pregnancy, which she subsequently terminated.

Discussion

Wilson's disease is an autosomal recessive disorder that impairs the body's ability to metabolize copper, leading to copper toxicity, particularly in the brain and liver, which manifests in a spectrum of hepatic, neurological, and psychiatric symptoms.[2,3] The disorder is attributed to mutations in the ATP7B gene, responsible for copper transport within the body.[3] Dysfunction in this gene results in the accumulation in the liver, with subsequent release into the bloodstream in its free form, rather than elimination via bile.[4] Copper accumulation during pregnancy can adversely affect both the mother and the developing fetus and is associated with complications, including spontaneous miscarriages, gestational diabetes, macrosomia (large birth weight), intrauterine growth restriction, and congenital anomalies.[2,5,6] Copper deposition

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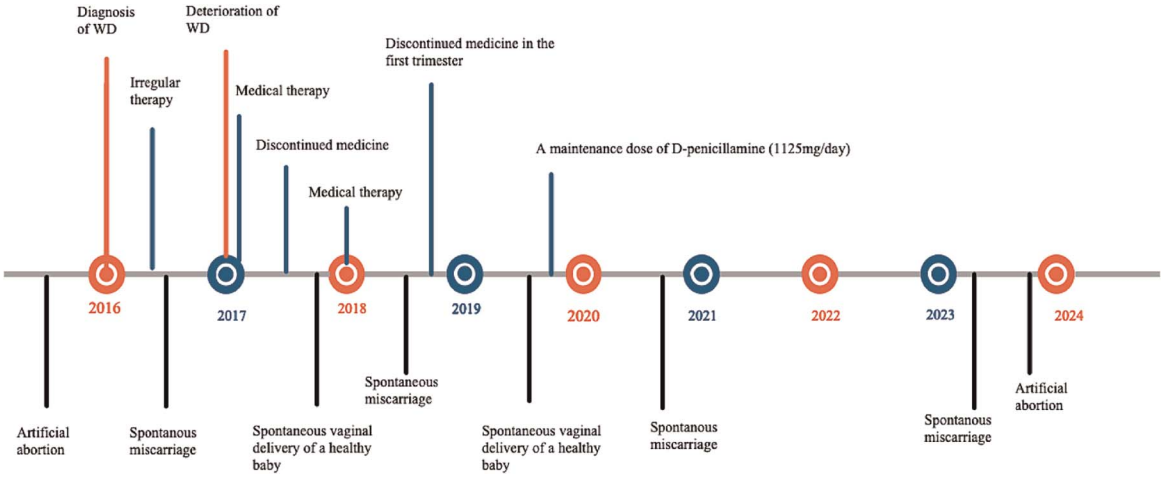

Figure 1. The timeline of the patient's pregnancies and treatments. WD: Wilson's disease.

in the placenta and fetal liver is implicated in these adverse outcomes.[7] Management of WD is contingent upon the patient's copper status and clinical presentation. Treatment typically involves the administration of copper-chelating agents, such as D-penicillamine or triethylenetetramine (trientine) to facilitate the removal of excess copper. Alternatively, zinc therapy, which inhibits copper absorption in the gastrointestinal tract, may be employed. These therapeutic strategies aim to mitigate the toxic effects of copper accumulation and enhance overall health outcomes.[8]

WD and pregnancy

In the published literature, 387 cases of WD during pregnancy have been reported (Table 1). The spontaneous miscarriage rate in the general population ranges from 10% to 20%.

Table 1

Comparative analysis of pregnancy outcomes across different studies.

Pregnancy outcome	Dathe *et al.*[9]	Tarnacka *et al.*[10]	Sinh *et al.*[11]	Yu *et al.*[12]	Reuner and Dinger[13]	Walshe[14]	Walshe[15]	Brewer *et al.*[16]	Scheinberg and Sternlieb[17]	Toaff *et al.*[6]	Marecek and Graf[18]
No. of patients	20	46	16	75	22	10	7	19	18	10	8
No. of pregnancies*	20	107	59	117	32	20	11	26	29	20	11
Initial WD manifestation†											
Hepatic	-	-	4	-	5	-	-	3	3	-	1
Neurologic	-	12	6	-	4	-	-	8	8	8	-
Hepatic + Neurological	-	-	5	-	5	-	-	-	-	2	-
Asymptomatic	-	78	-	-	8	3	-	7	4	-	7
Liver cirrhosis	-	-	5	-	-	1	-	-	-	1	-
WD therapy‡											
DPA	9	10	-	-	13	8	-	-	27	10	-
Trientine	2	-	-	-	4	-	11	-	-	-	-
Zinc	-	15	-	-	1	-	-	24	-	-	-
Combination	8	-	15	-	-	-	-	2	-	-	-
Discontinuation during pregnancy	1	-	-	97	1	10	-	-	2	1	7
No therapy	-	82	44	20	3	2	-	-	-	9	4
Pregnancy outcome§											
Alive	16	82	30	108	31	15	9	26	29	12	12
Healthy	16	78	30	108	31	15	8	24	29	12	12
Birth defect	-	4	-	-	-	-	1	2	-	-	-
Spontaneous miscarriage	3	20	24	9	1	3	1	-	-	8	-

*Total number of pregnancies across all patients.

†The number of patients with different initial Wilson's disease manifestations.

‡The number of patients takes the therapy during pregnancies.

§The number of pregnancy outcomes.

DPA: D-penicillamine; WD: Wilson's disease; –: Not applicable.

However, patients with WD may experience a higher rate, between 30% and 40%. In the present study, which included 734 pregnancies among 387 patients, the spontaneous miscarriage rate was determined to be 19%, suggesting that effective therapies can mitigate the incidence of spontaneous miscarriage.[19] In 1975, Schienberg hypothesized that the elevated miscarriages and infertility rates in patients with WD could be attributed to excessive levels of free copper in the uterus, which is similar to the mechanism of copper-containing IUDs.[20] However, Toaff later argued that active copper IUDs do not elevate serum copper and ceruloplasmin levels due to lack of systemic absorption.[21] Conversely, Gerald Oster *et al*.[22] demonstrated that intravenous copper salt administration in animal models (approximately 20 mg per kilogram) could induce ovulation or pseudopregnancy, likely due to copper-induced prostaglandin production, which increases uterine motility and impacts other smooth muscles, thereby leading to miscarriage and inhibiting implantation. Among 250 untreated cases, the spontaneous miscarriage rate was found to be 37%. However, the introduction of anti-copper therapies significantly reduced the spontaneous miscarriage rate to 14%. Studies have further indicated that the lowest spontaneous miscarriage rates were observed in patients who temporarily discontinued therapy, with most patients ceasing treatment after the first trimester. In our clinical case, irregular therapy resulted in 4 spontaneous miscarriages out of 8 pregnancies, with the most recent miscarriage occurred during high-dose D-penicillamine treatment.

WD and fetal defects

Patients with WD frequently discontinue or reduce medication use before or during pregnancy due to concerns about fetal teratogenicity.[23] In our study, however, we observed one case of fetal abnormality in a patient who had discontinued treatment. When comparing outcomes, the rate of fetal defects was lower in patients who stopped taking medication during pregnancy compared to those who continued (0.7% *vs*. 1.7%). The fetal defect rate among untreated patients was 1.4%, while those undergoing D-penicillamine therapy exhibited a defect rate of 2.3%. Notably, a 1971 case report identified D-penicillamine, which crosses the placental barrier, as a potential inducer of fetal malformations.[24] Subsequent studies have demonstrated that high doses of D-penicillamine are closely associated with an elevated risk of fetal defects.[23] During pregnancy, the maternal demand for copper increases, and insufficient copper intake may contribute to fetal abnormalities. Mark-Savage's study suggested that such abnormalities can persist even with copper supplementation aimed at normalizing serum levels, although their frequency decreases significantly.[23] The American Association for the Study of Liver Diseases Guidelines recommended reducing chelating agents by approximately 25–50% of the pre-pregnancy dose.[4] Previous recommendations have advised continuing D-penicillamine therapy at a dose below 0.5 g/d.[21,25] Given D-penicillamine's potential to impair wound healing, a dosage reduction in the third trimester is recommended if a cesarean section is necessary.[2,24] For presymptomatic patients or those on maintenance therapy, zinc is considered a safe and effective treatment option. Although there is no definitive evidence that switching to zinc therapy prior to conception reduces the risk of miscarriage or birth defects,[2] our review found that combination therapy resulted in no fetal defects during pregnancy. Consequently, combination therapy is regarded as the optimal choice for symptomatic patients with hepatic or manifestations of WD.[21]

WD and obstetric complications

While patients who do not take medication during pregnancy may experience spontaneous miscarriages and fetal defects, they are also at risk for life-threatening complications such as preeclampsia, placental abruption, liver failure, and HELLP syndrome.[21,26] Shimono *et al*.[26] reported a case in where a patient successfully delivered her first and second children while consistently taking D-penicillamine. However, she discontinued the medication during her third pregnancy due to worsening cirrhosis and ultimately succumbed to fulminant hepatic failure after delivery. In Avcioglu SN's case report,[27] a patient who had adhered to D-penicillamine throughout her pregnancy discontinued the drug only in the final 3 days, precipitating acute liver failure. Saito *et al*.[28] study documented a case where emergency cesarean delivery was necessitated by severe coagulopathy, thrombocytopenia, and obstetric disseminated intravascular coagulation. Increased hepatic copper deposition may contribute to the pathogenesis of preeclampsia and intrauterine growth restriction.[29] Liver transplantation remains the recommended first-line therapy for patients with decompensated liver cirrhosis, with successful pregnancies following transplantation for WD reported in previous cases.[28] Furthermore, a case of placental abruption was documented, despite the patient remaining asymptomatic while on D-penicillamine therapy at 37 weeks of gestation.[30]

In most treated patients, histopathological examination of placental membranes and the umbilical cord revealed no copper deposits, and additional copper staining yielded negative results. Infants' blood copper levels and hemoglobin concentrations were within normal ranges. However, in an untreated patient with worsening liver cirrhosis, placental histology revealed copper accumulation on the maternal side. Additionally, gestational diabetes mellitus is an increasingly prevalent concern in patients with WD, warranting oral glucose tolerance testing in all pregnant women with the condition. In this case, the patient remained asymptomatic throughout her pregnancies, with no observed complications. Fetal growth, as tracked by pregnogram, remained within the normal limits, and despite the patient's suboptimal weight gain, no intrauterine growth restriction was detected.

WD and delivery

The mode of delivery should be determined by the physical condition of the pregnant woman. Vaginal delivery is recommended for healthy, asymptomatic women, while cesarean section should be reserved for emergencies or cases with maternal complications. It is important to note that D-penicillamine is excreted in breast milk and may disrupt the infant's copper metabolism. Therefore, breastfeeding should be avoided, or D-penicillamine should be replaced with zinc.

Conclusion

A high rate of spontaneous miscarriage has been observed in patients with WD. However, effective medical therapy can significantly improve fertility and support successful pregnancies. Untreated patients face an elevated risk of maternal complications or mortality. In presymptomatic or maintenance-

treated patients, zinc is considered a safe and simple treatment option. Combination therapy has not shown fetal defects during pregnancy and is regarded as the optimal choice for all symptomatic patients with hepatic or neurological disease.

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Conflicts of Interest

None.

Data Availability

The datasets generated during and/or analyzed during the current study are publicly available.

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