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REVIEW

Wilson disease and pregnancy

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Wilson disease (WD, also known as hepatolenticular degeneration) is an inherited autosomal recessive disorder that affects copper metabolism, with a prevalence of roughly one case per 30,000 live births.[1] Copper is an essential component of our diet because it is an important cofactor for many proteins. The recommended intake is 0.9 mg/d and is primarily acquired from eating organic meats, seafood, and nuts.[2] Once ingested and absorbed by enterocytes, mainly in the duodenum, it is transported by the portal system and removed from the bloodstream via hepatocytes mediated by ATP7B. This ATPase regulates the transport of copper into the liver and incorporates copper atoms into apoceruloplasmin to form ceruloplasmin, which is then excreted into the bloodstream.[3] In WD, the absent or impaired function of the ATP7B gene leads to a decreased ability of copper to be excreted from the liver (via ceruloplasmin). This results in toxic amounts of copper accumulating in the liver and, eventually, as copper is released into the bloodstream, depositing into other organs such as the brain.

The majority of patients with WD are diagnosed in the first few decades of life, and about 5% develop acute liver failure, which occurs predominantly in young female patients (female: male ratio of 4:1).[4,5] According to a registry study in 2011 of 627 patients, women were more likely to present with hepatic symptoms compared to men (58% vs. 42%, $p < 0.01$).[6]

Besides the main presentation of WD, such as liver and neurological disease, female patients can present with oligomenorrhea, irregular menses, subfertility, or spontaneous miscarriage.[7] This is thought to be caused by copper deposition in the uterus.[8] Therefore, it is recommended that women undergo preconception counseling to discuss both medication options for a successful pregnancy and, if there is concern for WD inheritance, prenatal or preimplantation genetic testing. However, the utility of genetic testing is still unclear, given the possible harm to the embryo.[9]

Current goal-directed treatment for WD primarily involves lifelong oral pharmacotherapy. There is insufficient data demonstrating the benefit of low copper diets in WD without pharmacological co-treatment.[10] The purpose of pharmacotherapy is 2-fold: to minimize disease progression, which in turn improves fertility. In a study done in 2020 by Iorio and colleagues, a small cohort of WD patients were treated for at least 5 years and compared to healthy controls (both male and female patients). They found that female patients with proper disease control had minimal impairments in their fertility potential.[11] In 2018, Pfeiffenberger et al[12] retrospectively analyzed 130 patients with WD and 257 pregnancies, comparing spontaneous abortion rates among patients who were asymptomatic, had hepatic complications, or had neurological complications at the time of diagnosis to that of the general population. Figure 1 shows a higher rate of spontaneous abortion by the severity of WD at initial presentation.[12]

The main pharmacological treatment options for WD are D-penicillamine, trientine, and zinc. D-penicillamine and trientine work as chelators leading to cupruria. Zinc's mechanism of action for WD involves blocking copper absorption from various sites in the gastrointestinal tract. Patients must remain on pharmacotherapy throughout pregnancy, or else interruptions can result in acute liver failure or disease progression.[10] In the 2018 Pfeiffenberger study, spontaneous abortion rates were also reported among patients with 174 pregnancies while taking D-penicillamine, trientine, or zinc.[12] Spontaneous abortion rates among patients taking D-penicillamine or zinc were found to be the

Abbreviation: WD, Wilson Disease.

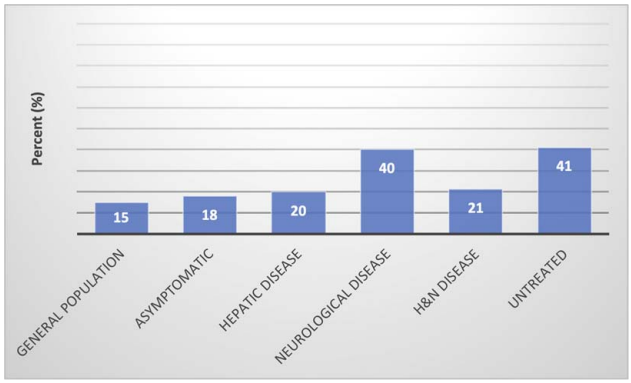

FIGURE 1 Comparing spontaneous abortion rates (%) in patients with WD based on initial presentation to the general population.[12] With n = number of pregnancies: asymptomatic group n = 38, hepatic group n = 113, neurological group n = 77, hepatic and neurological group n = 29, and untreated group n = 86. Abbreviation: H&N disease, hepatic and neurological disease. Adapted with permission from Pfeiffenberger et al.[12]

lowest among all therapy groups and statistically significant (n = 118, relative risk = 0.416, $p = 0.001$ in the D-penicillamine group vs. n = 20, relative risk = 0.246, $p = 0.035$ in the zinc group, abortion rate 17% vs. 10%, respectively). In the trientine group, there were 36 pregnancies, and the spontaneous abortion rate was 28%.

D-penicillamine has been successfully used in pregnancy, although there are reports of birth defects. Several studies followed pregnant women undergoing D-penicillamine therapy, which caused birth defects (Table 1). The reported birth defects included connective tissue disorders, low-set ears, and micrognathia.[7,9]

Trientine has also been well tolerated during pregnancy. Table 1 lists the percent of birth defects in pregnant women taking trientine therapy from several studies. The birth defects described were a glucose 6-phosphate dehydrogenase deficiency and a chromosomal defect in isochromosome X.[12,17]

Zinc has been shown to be the most tolerated during pregnancy, with the lowest amount of documented birth defects based on current literature (Table 1). Documented birth defects included a heart defect and microcephaly.[14]

It is hypothesized that chelator therapy (D-penicillamine or trientine) causes copper deficiency, leading to birth defects. Therefore, the recommended lowest effective dose during pregnancy is 50% less than the preconception dose while monitoring maternal liver tests. If cesarean delivery is recommended, patients taking D-penicillamine should reduce their daily dose further to 250 mg for 1–6 weeks prior to the planned surgery until roughly 6 months after to prevent delayed wound healing.[7] After vaginal delivery, preconception dosing can be resumed after wound healing. The mechanism for birth defects from zinc therapy is unclear, and there are currently no recommendations to adjust the dose during pregnancy[10] (Table 2). There are no specific guidelines on how to evaluate for therapy maintenance during the peripartum period, although it is recommended to follow maternal liver tests and 24-hour copper concentrations in the urine and blood at least once per trimester.[10]

There is limited safety data regarding breastfeeding while on pharmacological therapy for WD, although it is postulated that because ATP7B is found on mammary tissue, concentrations of copper in breast milk may be inadequate for mothers on chelating therapy.[10] A study in Japan by Kodama and colleagues in 2021 compared mean copper concentrations in breast milk among 18 mothers with WD treated with zinc, D-penicillamine, and trientine versus 25 controls. Mean copper concentrations among those being treated for WD were within the normal range, while zinc concentrations were significantly elevated among mothers with WD on zinc therapy.[18]

WD is an autosomal recessive disease that is typically diagnosed in the first few decades of life. Hence, it can impact women during pregnancy. Treatment for WD should begin as soon as possible

TABLE 1 Comparing birth defects in pregnant patients using D-penicillamine, trientine, or zinc therapy

Study author	Percent birth defects D-penicillamine (%)	Percent birth defects trientine (%)	Percent birth defects zinc (%)
Walshe[13]	0[a]	1	NA
Brewer et al[14]	NA	NA	8
Malik et al[15]	NA	NA	0
Dathe et al[16]	NA	0[b]	NA
Vishnupriya et al[6]	0	NA	0
Pfeiffenberger et al[12]	3	3	0
Reuner and Dinger[8]	0	0	0

Note: Total number of pregnancies in each group not available.
[a]One baby passed due to prematurity.
[b]One pregnant patient had co-therapy with zinc.
Abbreviation: NA, no data from study.

TABLE 2 Summary of pharmacological options for Wilson disease during pregnancy[4,10]

Drug	Dose adjustments	Safe during pregnancy?	24-urine copper goal	Safe while breastfeeding?
D-penicillamine	Decrease by ~50% to lowest effective dose from first trimester until postpartum wound healing; 250 mg daily 1–6 weeks prior to cesarean delivery	Limited safety data; monitor liver enzymes, 24-h urine copper, and physical exam	> 1000–2000 μg initially, then 200–500 μg	Limited safety data, avoid use
Trientine	Decrease by ~50% to lowest effective dose from first trimester until postpartum wound healing	Limited safety data, monitor as above	> 1000 μg upon initiation, then 150–500 μg	Limited safety data, avoid use
Zinc	Not needed, can continue 25–50 mg tid	Yes, monitor as above	< 100 μg	Limited safety data, avoid use

and preferably prior to pregnancy to greatly reduce the risk of spontaneous abortion. Zinc therapy is the safest during pregnancy, given the low percentage of documented birth defects. Breastfeeding while on therapy for WD involves potential harm to the newborn due to minimal safety data and, therefore, is not recommended at this time.

CONFLICTS OF INTEREST

Dhiren A. Shah owns stock in Gilead and AbbVie. David Weinstein has no conflicts to report.

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