Which treatment strategy is recommended in patients with WD during pregnancy and breastfeeding?

Recommendation

- Any anti-copper therapy should be maintained during pregnancy and breastfeeding **(LoE 4, weak recommendation, consensus).**

Reproductive health is a major need for women with childbearing potential living with WD. Untreated WD is associated with infertility, miscarriage, premature birth and perinatal mortality.[66] Of more than 800 reported pregnancies from around 450 women affected by WD, 21.7% resulted in spontaneous abortions, and almost 70% of these cases occurred in untreated patients.[277] Undiagnosed women have a 2.8-fold higher risk of miscarriage compared to treated patients with an established WD diagnosis.[278] Also, maternal health status can be affected by pregnancy. While a limited and transient elevation in liver enzymes can occur in pregnant women with stable disease, severe hepatic deterioration has been observed almost exclusively in those with uncontrolled copper status, either naïve to anti-copper drugs[279,280] or following treatment discontinuation.[280] Neurologic deterioration only occurs in 1% of pregnancies but can be irreversible.[278,281] The benefit of anti-copper treatment during pregnancy clearly outweighs the risks to the foetus of potential teratogenicity or drug-induced copper deficiency. The overall proportion of stillbirths and birth defects in WD pregnancies is comparable to that expected in non-WD pregnancies. Evidence for the potential teratogenicity of D-penicillamine related to copper deficiency comes from animal studies,[282] and reports of birth defects in humans (*e.g.*, connective tissue defects) are related with the highest dosage.[283–285] Similarly, trientine teratogenicity in rats is mediated by the low foetal copper status,[286] but there are no safety concerns in pregnant women under standard dosage.[277,287] The speculative risk of over chelation affecting foetal outcomes has led to the conservative recommendation to reduce the dose of copper-chelating agents during the first trimester.[46,173,277,278,287] Zinc is usually considered safe in pregnancy, although birth defects in zinc-treated women have been reported.[288,289]

Women with WD willing to conceive or who are pregnant should be carefully followed and supported to start or maintain anti-copper drug treatment. Intrauterine devices should be avoided.

Limited information indicates that D-penicillamine and trientine have no substantial passage in breast milk.[290] Neither copper-chelating agents nor zinc substantially affect the copper content of breast milk.[291] Thus, there is no evidence to contraindicate breastfeeding in mothers treated with anti-copper drugs.

Which symptomatic treatment is recommended in patients with WD and neurological and/or neuropsychiatric manifestations?

Recommendations

- Specific treatment for WD (chelators and zinc salts) enables improvement of neurological and neuropsychiatric symptoms but may be insufficient to control symptoms, in which case symptomatic treatments should be considered **(LoE 2, strong recommendation, strong consensus).**
- Symptomatic treatments of neurological symptoms should be based on pharmacotherapy, botulinum toxin injections, physiotherapy, speech therapy and rarely neurosurgery **(LoE 2, strong recommendation, strong consensus).**
- Neuropsychiatric symptoms can be treated by psychotropic medications (mood stabilisers, antidepressants, anxiolytics) and/or psychotherapy. Neuroleptics should be avoided (except quetiapine or clozapine) as they could worsen neurological symptoms **(LoE 2, strong recommendation, strong consensus).**

In addition to anti-copper therapy, symptomatic treatments are crucial at any stage of the disease for the long-term management of patients with WD who present neurological or psychiatric symptoms.[40,115,292–295]

The symptomatic treatment of neurological symptoms depends mainly on the predominant symptoms and includes pharmacotherapy, toxin botulinum injections, physiotherapy, and speech therapy. In rare situations, neurosurgical procedures may also be considered.[292] Symptomatic treatments need to be regularly adjusted to address the evolving nature of symptoms throughout the progression of the disease. Factors such as stress, concurrent medication use, trauma, or infections may exacerbate neuropsychiatric symptoms, displaying classical daily fluctuations, and should be taken into consideration.

Table 8 summarises the main therapy proposed for each symptom. The majority of these treatment proposals come from case reports.

Tremors

In cases of action/postural tremor, the most effective pharmacological treatment option is propranolol (20–240 mg/day, divided into two or three doses), followed by primidone (25 mg/day up to 750 mg daily in three divided doses).[296,297] If these treatments prove ineffective, benzodiazepines (alprazolam 0.75–1.5 mg/day) or clonazepam (0.5–4 mg/day) may offer some relief.[297] High dose zolpidem was effective in "wing beating" tremor in a case report.[298] For voice tremors, the optimal treatment involves the use of botulinum toxin A (BTX) with laryngeal electromyography-guided injections. BTX injections are also the preferred first-line treatment for dystonic tremors affecting the head, jaw, or voice.[299] Dystonic hand tremors should initially be addressed with anticholinergics or beta-blockers. In the event of treatment failure, second-line medications include benzodiazepines, primidone, or tetrabenazine. Intention, rubral or resting tremor are rare in WD and typically unresponsive to pharmacotherapy. In the case of severe disability due to tremor, and after long-term anti-copper treatment, deep brain stimulation (DBS) of the subthalamic regions or thalamus or thalamotomy, should be considered in light of the promising outcomes from several single case reports, but more studies are needed.[300–304]

Dystonia

Dystonia is one of the most disabling symptoms of WD and is often refractory to anti-copper treatment, with an unfavourable prognosis.[305] Focal dystonias are usually effectively treated with BTX injections[306–310] and segmental or generalized dystonias are treated with oral drugs alone or in combination with